FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN

A Dissertation Submitted to

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600032

In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

BRANCH - I - PHARMACEUTICS

Submitted by

BENCY SUSAN VARGHESE

Reg. No. 261510351

Under the guidance of

Mr. L. SUBRAMANIAN, M. Pharm., (Ph. D.,)

Associate Professor

DEPARTMENT OF PHARMACEUTICS

SANKARALINGAM BHUVANESWARI COLLEGE OF PHARMACY

ANAIKUTTAM, SIVAKASI – 626130.

OCTOBER – 2017

FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN

A Dissertation Submitted to

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600032

In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

BRANCH - I - PHARMACEUTICS

Submitted by

BENCY SUSAN VARGHESE

Reg. No. 261510351

Under the guidance of

Mr. L. SUBRAMANIAN, M. Pharm., (Ph. D.,)

Associate Professor

DEPARTMENT OF PHARMACEUTICS

SANKARALINGAM BHUVANESWARI COLLEGE OF PHARMACY

ANAIKUTTAM, SIVAKASI – 626130.

OCTOBER – 2017

CERTIFICATES

Fourrts
(India) Laboratories Pvt. Limited
Plant 1 : Vandalur - Kelambakkam Road, Kelambakkam - 603 103, Kancheepuram District, Tamil Nadu, India.
Phone : 91-44-4740 4310 E-mail : fourrts@plant.fourrts.com website : www.fourrts.com

CERTIFICATE

This is to certify that the dissertation entitled,**"FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN"**, submitted by **BENCY SUSAN VARGHESE (Reg no: 261510351)** to **The Tamilnadu Dr.M.G.R Medical University, Chennai** in partial fulfillment for the award of **"Master of Pharmacy in Pharmaceutics"**. The work described in this dissertation was carried out at **Research and Development Department of Fourrts (India) Laboratories Pvt. Ltd.,** under my supervision during the period of **February 2017 - April 2017.**

FOURRTS (INDIA) LABORATORIES PVT. LTD. RESEARCH AND DEVELOPMENT KELAMBAKKAM - 603 103

Dr.P.Ramkumar, M.Pharm., Ph.D.
Senior Manager-R&D Department,
Fourrts (India) Laboratories Pvt.Ltd,
Kelambakkam, Chennai-603 103,
Tamilnadu.

Corporate Office : No. 1, Fourrts Avenue, Annai Indra Nagar, Okkiyam Thoraipakkam, Chennai-600097, India.
Phone : 91-44-4344 1880 E-mail : admin@fourrts.com

Mr. L. SUBRAMANIAN, M. PHARM., (Ph.D.,)

Associate Professor

Department of Pharmaceutics,

Sankaralingam Bhuvaneswari College of Pharmacy,

Sivakasi– 626130,

Tamil Nadu.

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled, **"FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN"** submitted by **BENCY SUSAN VARGHESE (Reg. No. 261510351)** to **The Tamil Nadu Dr. M. G. R. Medical University, Chennai** for the award of the degree of **"MASTER OF PHARMACY IN PHARMACEUTICS"** is a bonafide record of the research work carried out by her partially in **Formulation and Research Development Department** of **FOURRTS INDIA Pvt. Ltd., Chennai**, under the supervision of **Dr. P.Ramkumar, M.Pharm., Ph.D.,** Head of Formulation Research and Development Department, **Fourrts India Pvt. Ltd., Chennai** and partially in the **Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi,** under my guidance and supervision. The content of this dissertation in full or in parts have not been submitted to any other Institute or University for the award of any degree or diploma.

Place: Sivakasi **Mr. L. Subramanian, M. Pharm., (Ph.D.,)**

Date:

Dr. M. RAJESH, M. Pharm., Ph.D.,

Professor and Head

Department of Pharmaceutics,

Sankaralingam Bhuvaneswari College of Pharmacy,

Sivakasi – 626130,

Tamil Nadu.

.

HEAD OF THE DEPARTMENT CERTIFICATE

This is to certify that the dissertation entitled**, "FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN"** submitted by **BENCY SUSAN VARGHESE (Reg. No. 261510351)** to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** for the award of the degree of **"MASTER OF PHARMACY IN PHARMACEUTICS"** is a bonafide record of research work carried out by her partially in **Formulation Research and Development Department** of **FOURRTS INDIA Pvt. Ltd., Chennai,** under the supervision of **Dr. P. Ramkumar, M.Pharm., Ph.D.,** Head of Formulation Research and Development Department, **Fourrts India Pvt. Ltd., Chennai** and partially in the **Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi,** under the guidance and supervision of **Mr. L. Subramanian, M.Pharm., (Ph.D.,) Associate Professor, Department of Pharmaceutics.** The content of this dissertation in full or in parts have not been submitted to any other Institute or University for the award of any degree or diploma.

Place: Sivakasi **Dr. M.Rajesh, M.Pharm., Ph.D.,**

Date:

Dr. P. SOLAIRAJ, M.PHARM, Ph.D.,

Principal

Sankaralingam Bhuvaneswari College of Pharmacy,

Sivakasi – 626130,

Tamil Nadu.

ENDORSEMENT CERTIFICATE BY THE PRINCIPAL

This is to certify that the dissertation entitled**, "FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN"** submitted by **BENCY SUSAN VARGHESE (Reg. No. 261510351)** to **The Tamil Nadu Dr. M. G. R. Medical University, Chennai** for the award of the degree of **"MASTER OF PHARMACY IN PHARMACEUTICS"** is a bonafide record of the research work carried out by her partially in **Formulation Research and Development Department,** of **FOURRTS INDIA Pvt. Ltd., Chennai,** under the supervision of **Dr. P. Ramkumar, M.Pharm., Ph.D.,** Head of Formulation Research and Development Department, **Fourrts India Pvt. Ltd., Chennai** and partially in the **Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi,** under the guidance and supervision of **Mr. L. Subramanian, M.Pharm., (Ph.D.,) Associate Professor, Department of Pharmaceutics.** The content of this dissertation in full or in parts have not been submitted to any other Institute or University for the award of any degree or diploma.

Place:Sivakasi **Dr. P. Solairaj, M.Pharm, Ph.D.,**

Date:

SANKARALINGAM BHUVANESWARI COLLEGE OF PHARMACY,
ANAIKUTTAM, SIVAKASI – 626130

GUIDE, HEAD OF THE DEPARTMENT AND PRINCIPAL CERTIFICATE

This is to certify that the dissertation entitled, **"FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN"** is a bonafide work done by **BENCY SUSAN VARGHESE (Reg. No. 261510351)** in the Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, Sivakasi in partial fulfillment of the university rules and regulations for the award of "**MASTER OF PHARMACY IN PHARMACEUTICS"** during the academic year 2016 - 2017.

Name & Signature of the Guide:

Name & Signature of the Head of Department:

Name & Signature of the Principal:

EVALUATION CERTIFICATE

This is to certify that the dissertation entitled, **"FORMULATION AND EVALUATION OF COLON TARGETED MATRIX TABLETS OF IBUPROFEN"** is a bonafide research work done by **BENCY SUSAN VARGHESE (Reg. No. 261510351)** to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** for the award of the degree of **"MASTER OF PHARMACY IN PHARMACEUTICS**" was evaluated by us during the academic year 2016-2017.

INTERNAL EXAMINER **EXTERNAL EXAMINER**

Date: **Date:**

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

Behind every successful venture, it is always said that there is an invisible force, which shape things in the right way and directions in which they should be. I found it my moral duty to bow to that driven power and ***THE ALMIGHTY*** *for imbibing in me the strength required for the successful completion of this dissertation work.*

As someone said, the future belongs to those who believe in the beauty of their dreams and I place my cordial thanks to ***my Father Mr. G.Geevarghese and my Mother Mrs. Beena Varghese and my sisters Mrs. Betcy Sanju and Miss. Blessy Susan Varghese*** *for giving me the opportunity to make my dreams come true and for their love without which I couldn't have reached this place.*

I owe my sincere thanks to our most respected ***Correspondent, Mr. S. Sriram Ashok, B.E.,*** *for providing necessary facilities to carry out this dissertation work successfully.*

I humbly owe my gratitude and sincere regards to my guide ***Prof. L Subramanian, M.Pharm., (Ph.D.,) Department of pharmaceutics, S.B College of Pharmacy****, Anaikuttam, for his valuable guidance, encouragement, untiring patience and support laid by him during all stages of my work. His keen interest, encouragement and fruitful suggestion have enabled me to make my work worthy of presentation.*

My sincere thanks to Industrial Guide ***Dr. P.Ramkumar, M.Pharm., Ph.D., Head of Formulation Research and Development Department, Fourrts India Pvt. Ltd., Chennai.*** *His continuous guidance and support have always propelled me to perform better. I am thankful to his constant source of encouragement and support, which provide to impetus and paved the way for the successful completion of this research work.*

It has been a privilege to work under the guidance of ***Mr. Shaik Shafi Quddin, M.Pharm., M.B.A., Asst. Manager of Formulation Research and Development Department, Fourrts India Pvt. Ltd., Chennai.*** *I owe my heartfelt and sincere thanks for his boundless enthusiasm. It gives me a great pleasure to thank his immense guidance, motivation, inestimable encouragement, dedicated involvement, optimist towards puzzling obstacles and unwavering support without whom, this work would not reach the present status.*

With deep sense of gratitude my thanks to ***Dr. S.Palanichamy, M.Pharm., Ph.D., Director and Professor, Department of Pharmaceutics, S.B College of Pharmacy****, for his kind blessings and unwavering support throughout this endeavor.*

I sincerely and specially thanks to ***Dr. M.Rajesh M.Pharm., Ph.D., Professor and Head, Department of Pharmaceutics, S.B College of Pharmacy****, for his support, guidance, suggestion, encouragement from the beginning to final stage of this work and opportunity to do my dissertation in industry.*

It is an honour to pay my respect and hearfelt thanks to ***Dr. P.Solairaj, M.Pharm., Ph.D., Principal, S.B College of Pharmacy*** *of our esteemed Institution for his valuable guidance, encouragement and support offered during my dissertation work.*

I am equally thankful to ***Dr. R.Sutharsingh, M. Pharm., Ph.D., Vice Principal and HOD of Pharmacognosy, S.B College of Pharmacy*** *for his help and suggestions during my dissertation work.*

I would like to express my sincere gratitude to ***Mr. S.C.Rajesh, M.Pharm., Asst. professor, Department of Analysis and Miss. A.Vigneshwari, M.Pharm., Assistant professor, Department of Pharmacology, S.B. College of Pharmacy*** *for their sensible help, suggestions and support for the successful completion of the dissertation work.*

I am truly indebted and deeply thankful to ***Miss. Lydia Benjamin and Mrs. Lalitha kumari*** *Industry staffs* ***Formulation Research and Development Department, Fourrts India Pvt. Ltd., Chennai*** *for their useful ideas, discussion, help and support throughout the research work.*

My sincere thanks to Industry staff especially ***Dr. P.Ramasubramaniyan, Mr. R.Deiveegan,, Mr. G.Thiyagarajan., Formulation Research and Development Department, Fourrts India Pvt. Ltd., Chennai*** *for their great effort and support for the successful completion of my work.*

*I express my hearty thanks to Mr****. J.Rajesh, Manager, Mrs. R.Chitra, Mr. A.Baskar Palraj, Mr. S.Vijay, and Mr. M.Purushothaman, Officers*** *of* ***Analytical Research and Development Department, Fourrts India Pvt. Ltd., Chennai*** *for their help and suggestions during my analytical work.*

I welcome this golden opportunity to express my heartfelt thanks to my senior ***P.Kamal Krishnan M.Pharm.,*** *for his most sincere suggestions in making my dissertation a success.*

I extend my special thanks to my dear friend ***Abin Alex M.Pharm.,*** *for his valuable help and support during this project work.*

I also extend my whole hearted thanks to ***Laboratory Assistant Mrs. Yasmin*** *of the P.G Department for her wonderful help and also I thank my teaching, non-teaching and administrative staffs for their kind co-operation.*

I also express my thanks to ***Abisha Flora*** *and* ***Julie Esther James*** *for their support and help for completing this dissertation work.*

Now at end of this acknowledgment I am not having words to thank for my M. Pharm classmates ***C.Santhanamariammal, R.Sujin and M.Vijayanand*** *for their Charmimg Company, kind co-operation and encouragement throughout my post graduation. They helped me in different ways and with whom I spent those moments in my life which are worth cherishing throughout my life.*

My acknowledgement is incomplete without a heartfelt thanks to all those people who are directly or indirectly contributed to this dissertation. If there is anyone I forget to put down their name on this paper, I apologize; it doesn't mean that they are not in my heart.

THANKS TO ALL….

BENCY SUSAN VARGHESE

(Reg. No. 261510351)

Dedicated To My Beloved Parents..

CONTENTS

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

S. No.	ABBREVIATION	EXPANDED FORM
1.	GIT	Gastro intestinal tract
2.	API	Active pharmaceutical ingredient
3.	HPMC	Hydroxy propyl methyl cellulose
4.	FDA	Food & Drug Administration
5.	HPMCP	Hydroxy propyl methyl cellulose phthalate
6.	PVAP	Poly vinyl acetate phthalate
7.	CAP	Cellulose acetate phthalate
8.	PHEMA	Poly hydroxy ethyl methyl acrylate
9.	PVA	Poly vinyl alcohol
10.	PVP	Poly vinyl pyrrolidone
11.	PEO	Poly ethylene oxide
12.	PA	Poly acrylamide
13.	PEG	Poly ethylene glycol
14.	PLA	Poly lactic acid
15.	PGA	Poly glycolic acid
16.	PCL	Poly capro lactone
17.	PDS	Poly dimethyl siloxane
18.	PEU	Poly ether urethane
19.	PVC	Poly vinyl chloride
20.	CA	Cellulose acetate
21.	EC	Ethyl cellulose
22.	CTDDS	Colon targeted drug delivery system
23.	NSAID	Non steroidal anti-inflammatory drug
24.	CFU	Colony forming unit
25.	IBD	Inflammatory bowel disease
26.	IV	Intra venous
27.	UC	Ulcerative colitis

28.	ANCA	Anti-neutrophil cytoplasmic antibody
29.	ADCC	Anti-body dependent cell mediated cytotoxicity
30.	NSAIA	Non steroidal anti-inflammatory agent
31.	HIS	In house standard
32.	FTIR	Fourier –Transform Infra Red
33	HCL	Hydrochloric acid
34.	CDDS	Colon specific drug delivery system
35.	DCL	Directly compressible lactose
36.	Ltd	Limited
37.	Eg	Example
38.	g/mol	Gram permole
39.	rpm	Rotations Per Minute
40.	ICH	International Conference Of Harmonization
41.	IP	Indian Pharmacopoeia
42.	°C	Degree Celsius
43.	Avg.wt	Average weight
44.	NaoH	Sodium hydroxide
45.	g/ml	Gram per milliliter
46.	%	Percentage
47.	NMT	Not more than
48.	NLT	Not less than
49.	LOD	Loss on drying
50.	Sec	Seconds
51.	Mg	Milligram
52.	Mm	Millimeter
53.	g/ml	Gram per milliliter
54.	USP	United States Pharmacopeia
55.	hrs	Hours
56.	UV-VIS	Ultraviolet–visible spectroscopy
57.	ml	Millilitre

58.	RH	Relative Humidity
59.	Nm	Nanometer
60.	SD	Standard deviation
61.	IHS	In house standards

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1. INTRODUCTION: [1-4]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration, belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery and the design of dosage forms must be developed within the intrinsic characteristics of GIT physiology, pharmacokinetics and pharmacodynamics and formulation design to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

1.1. TABLETS: [5]

Tablets are solid dosage forms each containing a unit dose of one or more medicaments. They are intended for oral administration. Some tablets are swallowed whole or after being chewed, some are dissolved or dispersed in water before administration and some are retained in the mouth where the active ingredient is liberated. Because of their composition, method of manufacture or intended use, tablets present a variety of characteristics and consequently there are several categories of tablets.

Tablets are usually solid, the end surfaces of which are flat or convex and the edges of which may be bevelled. They may exist in other shapes like triangular, rectangular, etc also. They may have lines or break-marks and may bear a symbol or other markings. They are sufficiently hard to withstand handling without crumbling or breaking.

Advantages of Tablets: [6]

- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- They are in general the easiest and cheapest to package and strip of all oral dosage forms.
- They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large-scale production than the other unit oral forms.
- They have the best-combined properties of chemical.
- Cost is low.
- Lighter and compact.
- Easy to swallowing with least tendency for hang-up.
- Sustained release product is possible by enteric coating.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and or monogrammed punch face.

Disadvantages of the tablets:

- Some drugs resist compression in to dense particles, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features are very challenging for the formulators.
- Difficult to swallow in case of children and unconscious patients.

- Bitter tasted drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

1.1.1. Various Types of Tablets: [7]

Based on the route of administration or the function, the tablets are classified as follows.

1) ***Tablets ingested orally.***

a) Compressed tablets
b) Multiple compressed tablets
    I) Layered tablets
    II) Compression coated tablets
c) Repeat action tablets
d) Delayed action and enteric coated tablets
e) Sugar and chocolate coated tablets
f) Film coated tablets
g) Chewable tablets

2) ***Tablets used in the oral cavity.***

a) Buccal tablets
b) Sublingual tablets
c) Troches and Lozenges
d) Dental cones

3) ***Tablets administered by other routes.***

a) Implantation tablets
b) Vaginal Tablets

4) ***Tablets used to prepare solution.***

a) Effervescent tablets
b) Dispensing tablets
c) Hypodermic tablets
d) Tablets triturates

1.1.2. PHARMACEUTICAL INGREDIENTS USED IN THE FORMULATION OF TABLETS:

a) *Acive ingredients*

A drug substance is the Active Pharmaceutical Ingredient (API) or component that produces pharmacological activity.

b) *Fillers/diluents*

Diluents are used as excipients for direct compression formulas have been subjected to prior processing to give them flow ability and compressibility.

Eg: Lactose, Dibasic calcium phosphate, Dextrose, Calcium carbonate, Magnesium carbonate, Starch, Sucrose, Mannitol.

c) *Binders*

Binders are agents which are used to impart cohesive qualities to the powdered material. Binders are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets.

Eg**:** Povidone, Acacia, Gelatin, HPMC, Polyvinyl pyrrollidone, Hydroxypropylcellulose.

d) *Disintegrants*

Disintegrants are substances or a mixture added to a tablet formulation to facilitate its breakup or disintegration of the tablet after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow rapid dissolution.

Eg**:** Microcrystalline cellulose, Starch, Crosscarmellose sodium, Sodium starch glycolate.

e) *Lubricants* [8]

During compression lubricants acts as to reduce the interface between the face of the die and the surface of the tablet and act to reduce the friction at this interface during ejection of the tablet from the tablet press. Inadequate lubrication of this interface results in the production of tablets with a pitted surface and is due to their ability of the tablet surface to detach from the surface of the tablet die. There are two main categories of lubricants: (1) insoluble and (2) soluble. Insoluble lubricants are added to the final mixing stage prior to the tablet compression.

Eg: Magnesium stearate, Stearicacid, Glycerylpalmitostearate.

Soluble lubricants are principally employed to overcome the possible deleterious effects of their insoluble counterparts on the time required for tablet disintegration and drug dissolution.

Eg: Polyethylene glycol, Polyethylene stearate, Lauryl sulphate salt.

f) *Glidants* [9]

Glidants are added to the formulation in order to improve the flow properties of the material to be fed into the die and sometimes aid in particle rearrangement within the die during the early stages of compression. They may act by interposing their particles between those of the other components and so, by virtue of their reduced adhesive tendencies, lower the overall interparticulate friction of the system.

Eg: Talc, Colloidal silicon dioxide.

g) *Adsorbents*

Adsorbents are used whenever it is required to include a liquid or semisolid component, e.g. a drug or a flavour, within the tablet formulation. As the production of tablets requires solid components, the liquid/semisolid constituent is adsorbed on to a solid component which, in many cases, may be one of the other components in the tablet formulation (e.g. diluent) during mixing. If this approach is not possible, an adsorbent is specifically included in the formulation.

Eg: Magnesium oxide/Carbonate, kaolin/Bentonite.

h) *Sweetening agents/flavours*

Sweetening agents and flavours (in accordance with other dosage forms) are employed to control the taste and hence the acceptability of tablets. These agents are of particular importance if the conventional tablet contains a bitter drug or, more importantly, if the tablet is a chewable tablet.

Eg: Aspartame, Sucralose, Sucrose, Glycerine, Mannitol, Sorbiltol, Acesulfame potassium.

Flavouring agents are incorporated into the formulation to give the tablet a more pleasant flavouror mask an unpleasant one. Eg: Chocolate, Peppermint, Pineapple and Vanilla flavour.

i) *Colours*

Colorants do not contribute to the therapeutic activity and to improve the product bioavailability or stability. Their main role is to facilitate identification and to enhance the aesthetic appearance of the product. All colorants used in pharmaceuticals must be approved and certified by the FDA. Some commonly used Pharmaceutical colorants are,

Eg: Erythrosine, Tartrazine, Sunset Yellow, Brilliant blue.

1.1.3. TABLET PROCESSING: [6]

Pharmaceutical products are processed all over the world using the direct compressing, wet granulation, or dry granulation methods. Method chosen depends on the ingredients, individual characteristics like flow property, compressibility etc. Right choice of method requires thorough investigation of each proposed ingredient in the formula for comprehensive approach for intractions and stability.

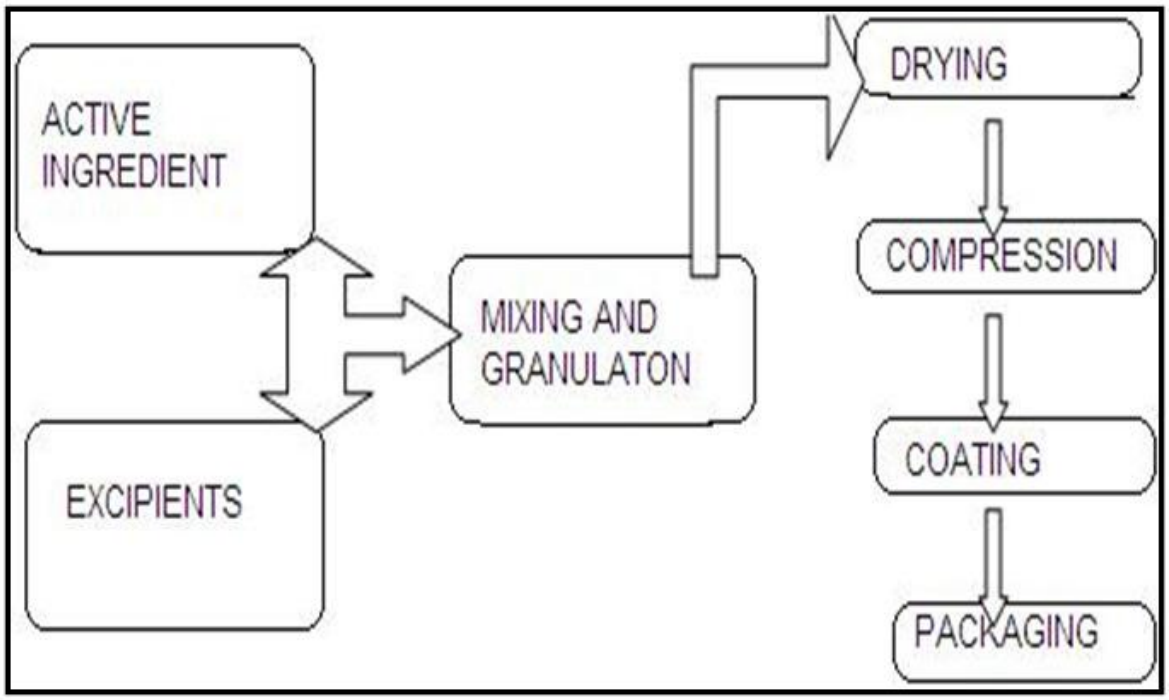


Figure.1. Various Unit Operation Sequences In Tablet Manufacturing

Table No:1 Tablet manufacturing methods – advantages and Limitations

Methods	Advantages	Limitations
Direct compression	Simple,Economical process No heat/moisture, good for unstable compounds.	Not suitable for all API, generally limted to lowerdose compounds Segregation potential Expensive excipients**.**
Wet granulation Aqueous	Robust process suitable for most compounds. Imparts flowability to a formulation. Can reduce elasticity problems. Coating surface with hydrophilic polymer can improve wet-ability. Binds API with excipients thus reduce in segregation potential.	Expensive, Time and energy consuming process. Specialized equipments required. Stability issues for moisture sensitive and thermolabile API with aqueous granulation.
Wet granulation Non- aqueous	Suitable for moisture sensitive API. Vacuum drying techniques can remove or reduce need for heat.	Expensive equipment. Need organic facility. Solvent recovery issues. Health and environment issues.
Dry granulation	Eliminates exposure to moisture and drying.	Dusty procedure. Not suitable for all compounds. Slow process.

1.1.4. MANUFACTURING DEFECTS IN TABLETS:

During the routine production of tablets, so many defects arise with the finished tablets which may be due to either some faults in the formulation or in the tablet equipment and sometimes due to both of these reasons. Some defects are noticed immediately during manufacturing, but others may be noticed on storage as in the case of capping. Therefore it is important to perform tests at the start and during production in order to make prompt remedial action. The defects are:

a) Defects during the processing of tablets are

- Capping
- Lamination
- Cracking

b) Defects due to excipients

- Picking
- Sticking
- Binding
- Chipping

c) Defects due to other factors are

- Mottling

d) Defects due to machine are

- Poor flow pattern
- Double impression

1.2. COATING OF TABLETS

The application of coating is usually based on one or more of the following:

- To mask the taste, odour or colour of the drug.
- To provide physical and chemical protection to the drug.
- To control the release of the drug.
- To protect the drug from the gastric environment of the stomach with an acid resistant coating.
- To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibility or to provide sequential drug release.
- To provide pharmaceutical elegance by use of special colour.

1.2.1. Types of coating:

1. Sugar coating
2. Film coating
3. Enteric coating
4. Extended release coating

Layers of coating in the formulation:

1. **Tablet core**
2. **Seal coating** acts as an inert intermediate layer between the core and outer layer (which are not compatible with one another).
3. **Enteric coating** acts as an outer layer which is resistant to gastric juice.

1.2.2. Enteric coatings: [10]

Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents once it reaches the small intestine. Their prime intension is to delay the release of drugs which are inactivated by the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa. The coatings that are used now a day to produce enteric effects are primarily mixed acid functionality and acid ester functionality, synthetic, or modified natural polymers. The most extensively used polymers are Cellulose acetate, polyvinyl acetate,

polyhydroxy propyl methyl cellulose, Methacrylic acid copolymers. All these polymers have the common feature of containing the dicarboxylic, pthalic acid in partially esterified form.

These polymers, being acid esters are insoluble in gastric media that have the pH of about 4. And then leave the stomach and enter into the duodenum (pH 4-6) and further along the small intestine, where the pH is increased to a range of (pH 7-8). The primary mechanism, by which these polymers lose their integrity, is there by admitting the releasing drug to the intestinal fluid. In this ionization of the residual carboxyl groups on the chain and subsequent hydration.

Important reasons for enteric coating are as follows:

* To protect acid-liable drugs from the gastric fluid.
* To protect gastric distress or nausea due to irritation from drug.
* To deliver drugs intended for local action in the intestines.
* To provide a delayed release component to repeat actions.
* Protect the drugs from harmful effect of the gastric contents; some of the drugs are prone to be hydrolyzed in acid media (Eg, omeprazole, pantaprazole)

Ideal enteric coating materials should have the following properties:

* Resistance to gastric fluids.
* Ready susceptibility to or permeability to intestinal fluids.
* Compatibility with most coating solution components and the drug substrates.
* The film should not change on aging.
* Formation of continuous film.
* Non-toxicity.
* Low cost.
* Ease of application.

1.2.3. Enteric Coating Materials:

Enteric coatings polymers are selectively insoluble substances. They won't dissolve in the acidic juices of the stomach, but they will when they reach the higher pH of the small intestine. Most enteric coatings won't dissolve in solutions with a pH lower than 5.5.

Commonly-used enteric coating polymers:

* Methacrylic acid copolymers
* Cellulose acetate (and its succinate and phthalate version)
* Polymethacrylic acid/acrylic acid copolymer

* Hydroxypropyl methyl cellulose phthalate (HPMCP)
* Polyvinyl acetate phthalate (PVAP)
* Hydroxy ethyl cellulose phthalate
* Cellulose acetate tetra hydro phthalate

The earliest enteric coatings utilized formalized gelatin, this was unreliable because of the polymerization of gelatin could not be accurately controlled. Another was shellac, disadvantage was polymerization with time, and resulting in poor dissolution of the coating. The most extensively used polymers are CAP, PVAP. The most recently used polymers are HPMCP, Methacrylic acid copolymers.

- **Cellulose Acetate Phthalate (CAP) :**

  Effective enteric coating, it only dissolves above pH 6 and may delay drug release longer than desired. It is permeable to moisture and simulated gastric fluid in comparison with other enteric polymers and it is susceptible to hydrolytic breakdown on storage.

- **Poly Vinyl Acetate Phthalate (PVAP) :**

  Less permeable to moisture and simulated gastric juice, it is more stable to hydrolysis on storage. Enteric dosage forms coated with PVAP disintegrates at pH 5.

- **Hydroxy Propyl Methyl Cellulose Pthalate (HPMCP):**

  It is available in two grades HP50 and HP55.

  HP55 solutions are more viscous than HP50.

  HP50 disintegrates at pH5 and HP55 disintegrates at pH5.5.

  It has stability similar to that of PVAP and dissolves in the same pH range. The advantage is that it does not require Plasticizer.

- **Methacrylic acid copolymers:** [11]

  Two grades are available A, B and C which differs in the ratio of free carboxyl to ester groups therefore:

  Type A - Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) has a ratio 1: 2: 0.2 and soluble in intestinal fluid from pH 6.

  Type B - Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) has a ratio of 1:2:0.1 and soluble in intestinal fluid from pH 7.

Type C - Poly (methacrylic acid, ethyl acrylate) 1:1 and soluble in intestinal fluid from pH 5.5.

1.3. EVALUTION OF TABLET

Tablets formulated may undergo physical and chemical changes thereby altering the bioavailability of the dosage form. The tablets are to be evaluated before dispensing to maintain their stability and bioavailability throughout its shelf life. Evaluation of tablets can be carried as follows:

a) Unofficial tests

- Tablet appearance
- Organoleptic properties
- Identification markings on tablet
- Size and shape of the tablet
- Thickness of tablet
- Hardness of tablet
- Friability of tablet

b) Official tests

- Weight variation test
- Content uniformity test
- Disintegration test
- Dissolution test.

1.4. MATRIX TABLET [12,13]

Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.

ADVANTAGES OF MATRIX TABLET:

- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improve the bioavailability of some drugs.
- Improve of the ability to provide special effects.

DISADVANTAGES OF MATRIX TABLET

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.

- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

1.4.1. CLASSIFICATION OF MATRIX TABLETS:

On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types.

1. Hydrophobic Matrices (Plastic matrices) [14]

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert. or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices[15]

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices[16]

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. A matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable

controlled release systems. The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups,

A. Cellulose derivatives: Methylcellulose 400 and 4000cPs, Hydroxy ethylcellulose; Hydroxy propyl methylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.

B. Non cellulose natural or semi synthetic polymers: Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

Polymers of acrylic acid: Carbopol-934, the most used variety.

4. Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by nonenzymetic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides

5. Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix[17-20]

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

1. Macro porous Systems: In such systems, the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Micro porous System: Diffusion may occurred in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3. Non-porous System: Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

1.4.2. POLYMERS USED IN MATRIX TABLET[21]

- **Hydrogels** Polyhydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA)
- **Soluble polymers** Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)
- **Biodegradable polymers** Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters
- **Non-biodegradable polymers** Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)
- **Mucoadhesive polymers** Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin
- **Natural gums** Xanthan gum, Guar gum, Karaya gum, Locust bean gum

1.4.3. EFFECT OF RELEASE LIMITING FACTOR ON DRUG RELEASE: [22-23]

The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

A. Polymer hydration:

It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B. Drug solubility:

Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable

aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C. Solution solubility:

In view of *in-vivo* (biological) sink condition maintained actively by hem perfusion, it is logical that all the *in-vitro* drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with *in-vivo* drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D. Polymer diffusivity:

The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion Ed has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallanity of polymer. The release of drug may be attributed to the three factors viz, i. Polymer particle size ii. Polymer viscosity iii. Polymer concentration.

i. Polymer particle size:

Malamataris stated that when the content of hydroxyl propyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxyl propyl methylcellulose led to the burst release.

ii. Polymer viscosity:

With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

iii. Polymer concentration:

An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the

effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

E. Thickness of polymer diffusional path:

The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

$$JD = D\ dc/dx$$

Where, JD is flux of diffusion across a plane surface of unit area

D is diffusibility of drug molecule,

dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

F. Thickness of hydrodynamic diffusion layer:

It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer δd.

G. Drug loading dose:

The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases. In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

H. Surface area and volume:

The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the *in-vitro* and *in-vivo* rate of the drug

release, are observed to be dependent upon surface area of dosage form. *Siepman et al.* found that release from small tablet is faster than large cylindrical tablets.

I. Diluent's effect:

The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J. Additives:

The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydrosoluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

1.4.4. BIOLOGICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET

- Biological half-life.
- Absorption.
- Metabolism
- Distribution
- Protein binding
- Margin of safety

1.5. COLON TARGETED DRUG DELIVERY SYSTEM

Colon Targeted Drug Delivery System (CTDDS) may be following the concept of Controlled or Sustained drug Delivery System. For CTDDS oral route of administration has received most attention. Local delivery allows topical treatment of inflammatory bowel disease. Colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs.[24-25]

For effective and safe therapy of these colonic disorders, colon specific drug delivery is necessary i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon[26]. Today, colon specific drug delivery is challenging task to pharmaceutical technologist. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons,

i. Less diversity,
ii. Intensity of digestive enzymes,

Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CTDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability[27]. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time[28]. Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery [29].

The bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the reaches the colon. Because the colon has a long residence time 72 hours and high water content it favors absorption of poorly absorbed drug molecule may have an improved bioavailability, CTDDS has been employ to achieve following objectives,

i) Sustained delivery to reduce dosing frequency

ii) Delay delivery of drug to achieve high concentration in treatment of disease of distal gut

iii) To delay deliver to a time appropriate to treat acute phase of disease

iv) Deliver drug to that region that is less hostile metabolically, drug which is acid and enzyme labile such as proteins[30].

Benefits of Colon Target Drug Delivery System[31-32]

a) Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, Crohn's disease etc.)
b) Minimizing extensive first pass metabolism of steroids.
c) High retention time thus increasing the bioavailability of poorly absorbable drugs.
d) Increased patient compliance.
e) Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
f) Decreases the side effects in the treatment of colon diseases.
g) Prevents gastric irritation resulting due to the administration of NSAIDs.
h) Minimizes first pass metabolism.
i) Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
j) Decreased frequency of administration. Hence decreased cost of drugs.
k) High retention time thus increasing the bioavailability of poorly absorbable drugs.
l) Targeted drug delivery to the colon in treatment of colonic disease ensures direct treatment at the affected area with lower dose and less systemic side effects.
m) The colonic drug delivery can also be utilized as the threshold entry of the drugs into blood for proteins and peptides which degraded or poorly absorbed in upper GIT.
n) The colon targeted drug delivery can also be used for chronotherapy for effective treatment of diseases like asthma and angina.
o) High retention time thus increasing the bioavailability of poorly absorbable drugs.

Limitations of colon target Drug Delivery System[31, 33]

a) Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
b) Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.
c) There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired CSDDS site.
d) The pH level in the small intestine and caecum are similar which reduces site specificity of formulation.
e) The major disadvantage of colonic delivery of drug is poor site specificity.
f) Diet and diseases can affect colonic micro flora which can negatively affect drug targeting to colon.
g) Nature of food present in GIT can affect drug pharmacokinetics.
h) Enzymatic degradation may be excessively slow which can cause interruption in polymer degradation and thus alters the release profile of drugs.

Need for colon targeting drug delivery: [34, 35, 36, 37]

- Targeted drug delivery to the colon to ensure that direct treatment at the disease site (local delivery), at lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine .

- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon .
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

1.5.1. ANATOMY AND PHYSIOLOGY OF COLON [38]

In GIT, large intestine starts from the ileocecal junction to the anus having a length of about 1.5m (adults) and is divided into three parts, viz. colon, rectum and anal canal. The colon consists of caecum, ascending colon, transverse colon, descending colon and sigmoid colon. Colon is made up of four layers, serosa, muscularis externa, submucosa and mucosa. The epithelium consists of a single layer of cells, which lines the crypts and covers the surface of the mucosa. Three major cell types found in the epithelium are the columnar absorptive cells, goblet (mucous) cells and entero endocrine cells. Adjacent columnar absorptive cells are attached to one another near apical margins by a junctional complex.

Mucus production in the colon is a function of goblet cells and the proportion of goblet cells increases in the elderly. The colon and the rectum have an anatomic blood supply. The arterial blood supply to the proximal colon is from the superior mesenteric artery and the inferior mesenteric artery supplies the distal colon. The venous drainage is via the superior (proximal colon) and inferior (distal colon) veins. The arterioles and capillary branches pass to the epithelial surface between the crypts and form an extensive network of capillary plexi. The mucus lining of GIT forms a barrier against bacterial invasion of the gut wall.

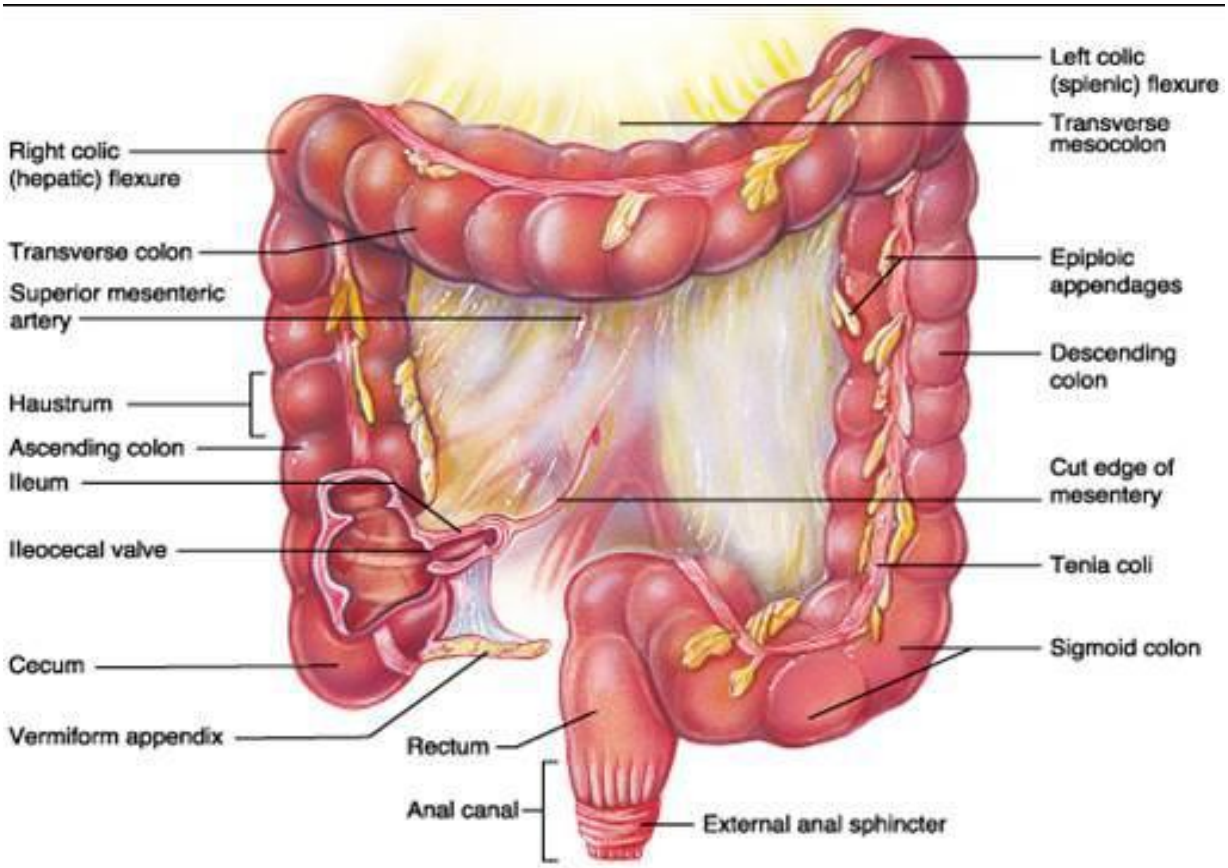


Figure: 2 Anatomy of Colon.

1.5.2. COLONIC MICRO FLORA [39]

The sluggish movement of material through the colon allows a large microbial population to succeed there. Over 400species of bacteria found, for the most part anaerobes and a small number of fungi. The bacterial count (colony forming unit/mL, CFU/mL) is 1011-1012CFU/mL in colon. Most of them are anaerobes. E.g.: Bacteroides, Bificlobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus and Clostridium; others are facultative anaerobes e.g.: E.Coli. Among all of them 20-30% are Bacteroides.

1.5.3. pH IN THE COLON

Radio telemetry has been used to measure the gastrointestinal pH in healthy human subjects. The average pH of the caecum and colon lumen is 6.8 – 7.0. The highest pH levels (7.5 – 8.0) were found in the terminal ileum. On entry into the colon, the pH dropped to 6.4 –7.0. The pH in the mid-colon was measured at 6.6 – 7.4 and in the left colon, 7.0 – 7.7. The fall in pH

on entry into the colon is due to the presence of short chain fatty acids arising from the bacterial fermentation of polysaccharides. Colonic pH has been shown to be reduced in disease.

1.5.4. FUNCTIONS OF THE COLON

The major function is the consolidation of the intestinal contents into feaces by the absorption of water and electrolytes. The absorptive capacity is very high. In healthy human colon, sodium and chloride ions are usually absorbed and potassium and bicarbonate ions are usually secreted. Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements caused by circular muscle and causing the appearance of the sac-like haustra, predominate and resulting in mixing of the luminal contents. Significant propulsive activity, associated with defecation and affected by longitudinal muscle, is less common and occurs an average of three or four times daily.

1.5.5. BARRIERS TO COLONIC DRUG ABSORPTION[38]

Drug absorption through the colon can be limited by number of barriers. In the lumen itself, specific and non-specific drug binding can occur through the interaction of drug with dietary components and products released from bacteria residing in the colon. The mucus barrier at the epithelial surface can present a formidable physical barrier to uptake as a result of specific and non-specific drug binding. Mucus-drug incompatibility can be compounded if the delivered drug stimulates the mucus secreting goblet cells because the transit through mucus is diffusion limited, the greater the thickness of this barrier, longer the time required for an individual molecule to reach the epithelial surface.

The unstirred water layer (the space between mucus layer and epithelial cells) presents another barrier to colonic absorption, particularly for lipophilic drugs. A pH gradient may also exist across the unstirred water layer. This lower pH at the colonocyte surface may dramatically alter drug solubility and since drug transport within the unstirred layer is driven by chemical potential, altered drug solubility can affect absorption. Probably the most significant barrier to epithelial transport of drugs in the colon occurs at the level of the epithelium. Here, the lipid bilayers of the individual colonocytes and the occluding junctional complex (OJC) between these cells provide a physical barrier to drug absorption.

1.5.6. FACTORS AFFECTING COLONIC DRUG DELIVERY

There are many factors that influence the drug delivery to colon. They include

1. Transit through GIT

In order to reach colon in an intact form, the drug delivery systems should surpass the barriers in the stomach and small intestine. Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hours to reach the ileocecal junction. During this period the dosage form is exposed to enzymes present in small intestine. Compared to the other region of GIT, movement of material through the colon is slow. The colonic transit time of a capsule in adult is 20-35 hrs. Improved residence time with subsequent longer transit time and the contact of dosage form with microflora in colon govern the release and absorption of drug from dosage form.

2. Gastric emptying

Once the dosage form enters the stomach, the primary concern is how long it will remain there before being discharged into the duodenum. Emptying generally completes in 5-10 min up to 2 hours depending on phase of the stomach at the time of drug administration. It is preferable for a colonic delivery system to spend little time in the stomach. Such system may release the drug at a distant locus from the colon.

3. Stomach and intestinal pH

The pH of GIT must be considered when enteric coatings (bioerodiblepolymers) are used to deliver drugs to colon. Since, in such systems, GIT pH gradient is used to trigger drug release.

4. Colonic microflora

Microflora of the colon has a number of implications in health and the treatment of diseases such as IBD. The concentration of gut microflora rises considerably in the terminal ileum to reach extraordinarily high levels in the colon. The gut bacteria are capable of catalysing a wide range of metabolic events. Many colon-specific drug delivery systems rely on enzymes unique to gut microflora to release active agents in the colon. However, only two or three enzyme systems namely azoreductases and glycosidases (including glucuronidase) have been explored in this area. A large number of polysaccharides are actively hydrolysed by gut

microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. The second class of enzymes used to trigger the release of drugs in the colon is glycosidases (including glucuronidases). The main bacterial groups responsible for β- glycosidases activity are *lactobacilli, bacteroides* and *bifidobacteria*.

5. Gastrointestinal Disease State

Gastrointestinal diseases such as IBD (inflammatory bowel disease), crohn's disease, constipation, diarrhoea and gastroenteritis may affect the release and absorption of drug from colon-specific drug delivery system.

1.5.7. COLONIC ABSORPTION

As absorption capacity of colon is very high which is attributed to the colon transit time, which can be as long as 20-35 hours, hence it is ideally suited for absorption. The absorption is influenced by the transport of water, electrolytes and ammonia across the mucus and it is more in the proximal colon than the distal colon. Drug molecules pass from the apical to basolateral surface of epithelial cells by

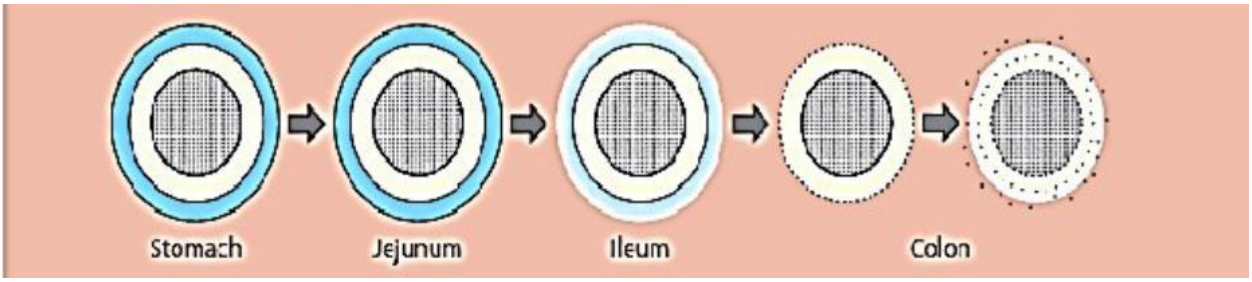


Figure: 3 Drug release pattern of coated system at different pH conditions in GIT

- Passing through colonocytes (trans cellular transport), or
- Passing between adjacent colonocytes (para cellular transport)

Small amphipathic drugs may pass this barrier through transcellular transport. Paracellular transport may be the most promising means of general drug absorption in colon. Additionally, carrier mediated uptake of the drug in the colon is not extensive and usually related to the metabolic events of the resident bacteria. Receptor mediated endocytosis and pinocytosis could, however lead to transcellular transport of drug.

1.6. INFLAMMATORY BOWEL DISEASE[40]

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. Crohn's disease and ulcerative colitis are the principal types of inflammatory bowel disease. It is important to note that not only does Crohn's disease affect the small intestine and large intestine, it can also affect the mouth, esophagus, stomach and the anus whereas ulcerative colitis primarily affects the colon and the rectum.

1.6.1. Ulcerative colitis[41]

Ulcerative colitis is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which starts in the rectum and generally extends proximally in a continuous manner through part of or the entire colon however, some patients with proctitis or left-sided colitis might have a caecal patch of inflammation. Bloody diarrhoea is the characteristic symptom of the disease.

Ulcerative colitis is a nonspecific inflammatory bowel disease of unknown etiology that effects the mucosa of the colon and rectum. The treatment of ulcerative colitis depends on the amount of the large bowel affected and the severity of the inflammation. If the disease is confined only to the lower part of the bowel, a mild attack may be treated with drugs (such as mesalazine or steroids) given directly into the rectum through the back passage (e.g.by an enema or suppositories). Ulcerative colitis is a chronic, or long lasting, disease that causes inflammation irritation or swelling and sores called ulcers on the inner lining of the large intestine. Ulcerative colitis most often begins gradually and can become worse over time. Symptoms can be mild to severe. Most people have periods of remission times when symptoms disappear that can last for weeks or years. The goal of care is to keep people in remission long term.

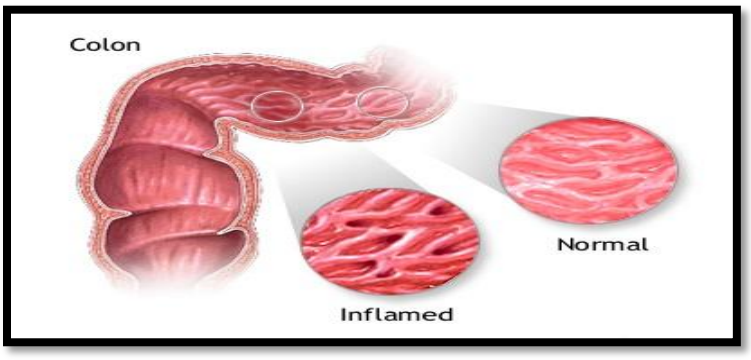


Figure: 4 Diagram of Inflamed and normal colon

1.6.2. Signs and symptoms of Ulcerative colitis

The most common signs and symptoms of ulcerative colitis are diarrhea with blood or pus and abdominal discomfort. Other signs and symptoms include

- An urgent need to have a bowel movement
- Nausea or loss of appetite
- Weight loss
- Fever
- Anemia is a condition in which the body has fewer red blood cells than normal

Less common symptoms include

- Joint pain or soreness
- Eye irritation
- Certain rashes

The symptoms a person experiences can vary depending on the severity of the inflammation and where it occurs in the intestine. When symptoms first appear,

- Most people with ulcerative colitis have mild to moderate symptoms
- About 10 percent of people can have severe symptoms, such as frequent, bloody bowel movements, fever and severe abdominal cramping

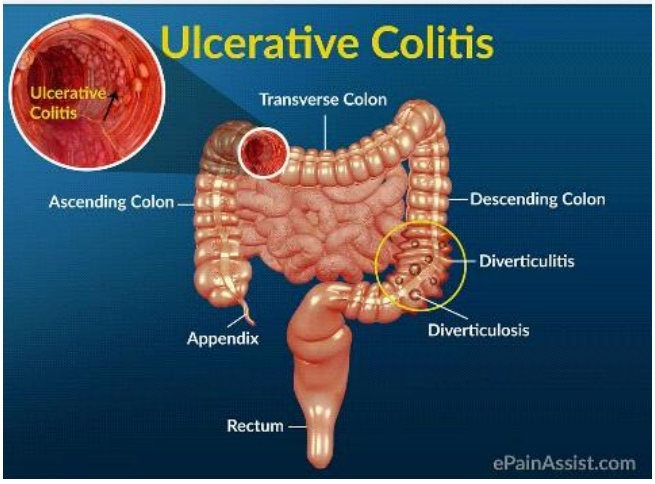


Figure: 5 Diagram of ulcerative colitis

1.6.3. CAUSES OF ULCERATIVE COLITIS[42]

The exact cause of ulcerative colitis is unknown. Researchers believe the following factors may play a role in causing ulcerative colitis:

- Overactive intestinal immune system
- Genes
- Environment

Overactive intestinal immune system.

Scientists believe one cause of ulcerative colitis may be an abnormal immune reaction in the intestine. Normally, the immune system protects the body from infection by identifying and destroying bacteria, viruses, and other potentially harmful foreign substances. Researchers believe bacteria or viruses can mistakenly trigger the immune system to attack the inner lining of the large intestine. This immune system response causes the inflammation, leading to symptoms.

Genes.

Ulcerative colitis sometimes runs in families. Research studies have shown that certain abnormal genes may appear in people with ulcerative colitis. However, researchers have not been able to show a clear link between the abnormal genes and ulcerative colitis.

Environment.

Some studies suggest that certain things in the environment may increase the chance of a person getting ulcerative colitis, although the overall chance is low. Nonsteroidal anti-inflammatory drugs, antibiotics, and oral contraceptives may slightly increase the chance of developing ulcerative colitis. A high-fat diet may also slightly increase the chance of getting ulcerative colitis.

Some people believe eating certain foods, stress, or emotional distress can cause ulcerative colitis. Emotional distress does not seem to cause ulcerative colitis. A few studies suggest that stress may increase a person's chance of having a flare-up of ulcerative colitis. Also, some people may find that certain foods can trigger or worsen symptoms.

1.6.4. INCIDENCE AND PREVALENCE OF ULCERATIVE COLITIS

Ulcerative colitis occurs worldwide. It is considered common in most of Europe and North America and uncommon in most of the developing Asian countries. The incidence/prevalence of ulcerative colitis varies not only according to geographical region but also with race and ethnicity.

How is ulcerative colitis diagnosed?

A health care provider diagnoses ulcerative colitis with the following:

- Medical and family history
- Physical exam
- Lab tests
- Endoscopies of the large intestine

Medical and Family History

Taking a medical and family history can help the health care provider diagnose ulcerative colitis and understand a patient's symptoms. The health care provider will also ask the patient about current and past medical conditions and medications.

Physical Exam

A physical exam may help diagnose ulcerative colitis. During a physical exam, the health care provider most often

- checks for abdominal distension, or swelling
- listens to sounds within the abdomen using a stethoscope
- taps on the abdomen to check for tenderness and pain

Lab Tests

A health care provider may order lab tests to help diagnose ulcerative colitis, including blood and stool tests.

Blood tests

A blood test involves drawing blood at a health care provider's office or a lab. A lab technologist will analyze the blood sample. A health care provider may use blood tests to look for

- Anemia
- Inflammation or infection somewhere in the body
- Markers that show ongoing inflammation
- Low albumin, or protein common in patients with severe ulcerative colitis

Stool tests.

A stool test is the analysis of a sample of stool. A health care provider will give the patient a container for catching and storing the stool at home. The patient returns the sample to the health care provider or to a lab. A lab technologist will analyze the stool sample. Health care providers commonly order stool tests to rule out other causes of GI diseases, such as infection.

Endoscopies of the Large Intestine

Endoscopies of the large intestine are the most accurate methods for diagnosing ulcerative colitis and ruling out other possible conditions, such as Crohn's disease, diverticular disease, or cancer. Endoscopies of the large intestine include

- Colonoscopy
- Flexible sigmoidoscopy

Colonoscopy

Colonoscopy is a test that uses a long, flexible, narrow tube with a light and tiny camera on one end, called a colonoscope or scope, to look inside the rectum and entire colon. In most cases, light anesthesia and pain medication help patients relax for the test. The medical staff will monitor a patient's vital signs and try to make him or her as comfortable as possible. A nurse or technician places an intravenous (IV) needle in a vein in the patient's arm or hand to give anesthesia. For the test, the patient will lie on a table or stretcher while the gastroenterologist inserts a colonoscope into the patient's anus and slowly guides it through the rectum and into the colon. The scope inflates the large intestine with air to give the gastroenterologist a better view. The camera sends a video image of the intestinal lining to a monitor, allowing the gastroenterologist to carefully examine the tissues lining the colon and rectum. The gastroenterologist may move the patient several times and adjust the scope for better viewing. Once the scope has reached the opening to the small intestine, the gastroenterologist slowly withdraws it and examines the lining of the colon and rectum again.

A colonoscopy can show irritated and swollen tissue, ulcers, and abnormal growths such as polyps extra pieces of tissue that grow on the inner lining of the intestine. If the gastroenterologist suspects ulcerative colitis, he or she will biopsy the patient's colon and rectum. A biopsy is a procedure that involves taking small pieces of tissue for examination with

a microscope. A health care provider will give patients written bowel prep instructions to follow at home before the test. The health care provider will also give patients information about how to care for themselves following the procedure.

Flexible sigmoidoscopy.

Flexible sigmoidoscopy is a test that uses a flexible, narrow tube with a light and tiny camera on one end, called a sigmoidoscope or scope, to look inside the rectum, the sigmoid colon, and sometimes the descending colon. In most cases, a patient does not need anesthesia. For the test, the patient will lie on a table or stretcher while the health care provider inserts the sigmoidoscope into the patient's anus and slowly guides it through the rectum, the sigmoid colon and sometimes the descending colon.

The scope inflates the large intestine with air to give the health care provider a better view. The camera sends a video image of the intestinal lining to a monitor, allowing the health care provider to examine the tissues lining the sigmoid colon and rectum. The health care provider may ask the patient to move several times and adjust the scope for better viewing. Once the scope reaches the end of the sigmoid colon, the health care provider slowly withdraws it while examining the lining of the colon and rectum again. The health care provider will look for signs of bowel diseases and conditions such as irritated and swollen tissue, ulcers, and polyps.

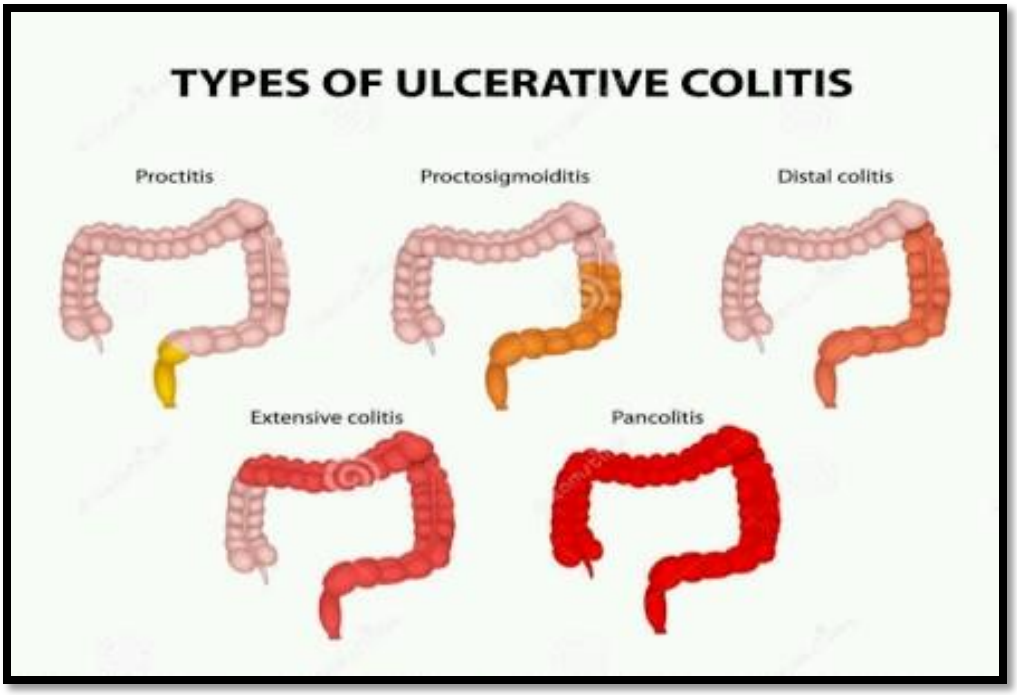


Figure: 6 Types of ulcerative colitis

- Proctitis – Involves only the rectum
- Proctosigmoiditis – Involves the rectum and sigmoid colon (the lower segment of the colon before the rectum)
- Distal colitis –Involve only the left side of the colon
- Pancolitis –Involves the entire colon
- Backwash ileitis – Involves the distal ileum

1.6.5. Pathophysiology of ulcerative colitis [43]

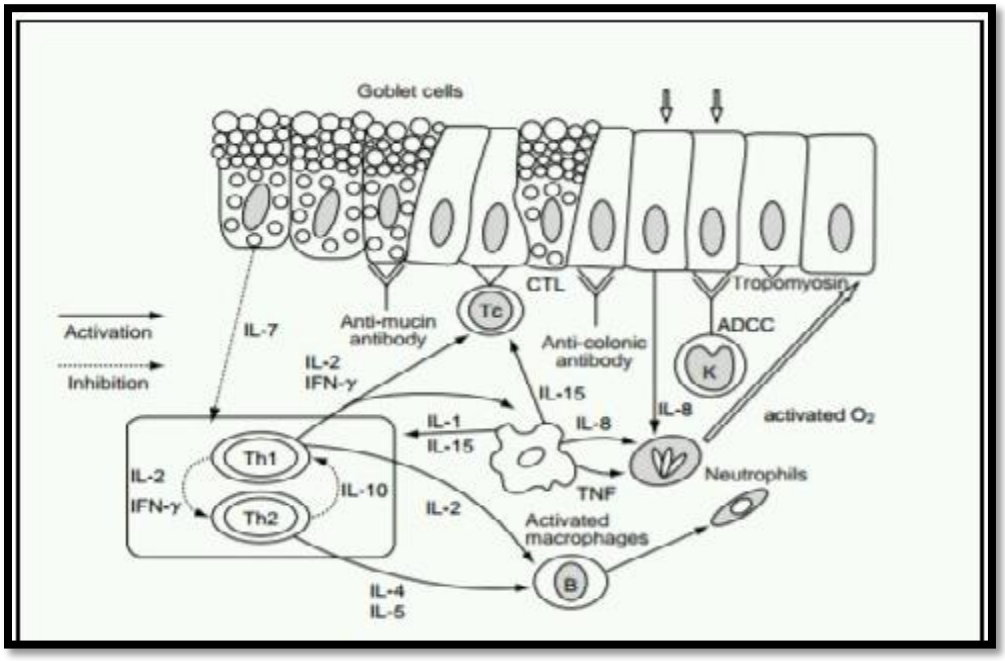


Figure: 7 Pathophysiology of ulcerative colitis

1. Antibodies and B cells

The pathophysiology of UC is shown in Fig. 7. An increase of lymphocytes, especially activated T cells and IgG-containing B cells, is seen in the colonic mucosa. This may induce the increased production of antibodies directed against intestinal antigens and auto antigens. In addition, a role of the type I allergic response has been suggested in the development of acute exacerbation. Auto antibodies, such as anti colon antibody and anti-neutrophil cytoplasmic antibody (ANCA), are detected in the serum of some UC patients and damage to the colonic mucosa is assumed to be due to antibody dependent cell-mediated cytotoxicity (ADCC) involving these auto antibodies. In other words, a functional abnormality of mucosal T cells and associated activation of antibody-producing cells seems to promote the local production of auto antibodies in the colonic mucosa that may contribute to the pathogenesis of this disease. However, these antibodies are not present in all patients and there is no correlation between such antibodies and disease activity or the duration of illness. Thus, it is possible that these antibodies may develop secondary to inflammation without any pathogenic activity. At the present time, therefore, there is not enough evidence about the role of autoimmunity in UC.

2. Cytokines and T cells

In the normal state, the mucosal immune system is involved in the suppression or inhibition of immune responses to the intestinal contents. The concept that this tightly regulated state is altered in UC has been proposed by many groups. Various abnormalities of the cytokine network occur in the colonic mucosa of UC patients, resulting in uncontrolled and sustained inflammation. We have focused on defective regulation of the differentiation and proliferation of the thymic T cell lineage in UC patients and have described a factor that affects the processing of thymic T cells. Purification of this factor revealed that it was IL-7. Because IL-7 produced by intestinal epithelial cells regulates the proliferation of mucosal T cells, disruption of this mechanism could lead to abnormal perpetuation of inflammation. There is considerable evidence that defective mucosal immunoregulation, including abnormal changes of T cells, B cells, granulocytes, mac-rophages, and the cytokines and chemokines produced by these cells, plays a major role in the pathogenesis of UC. The current need is to clarify the factors that lead to defective immunoregulation.

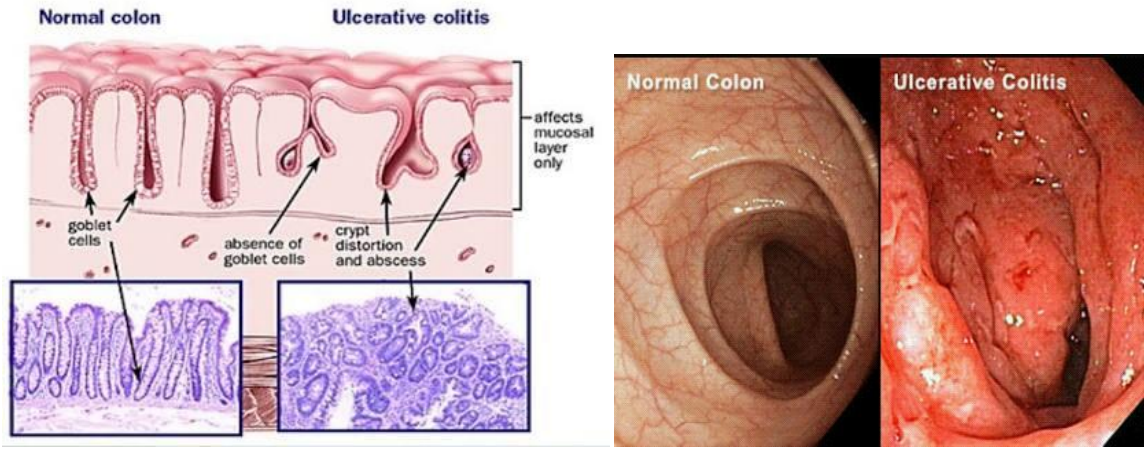


Figure: 8 Microscopical structure of ulcerative colitis

CHAPTER 2

AIM AND PLAN OF WORK

2. AIM AND PLAN OF WORK

2.1 AIM OF WORK

The aim of present study was to formulate the colon targeted matrix tablet of Ibuprofen and to evaluate the formulation for various parameter to release the active ingredient after predetermine time in a predetermine location with better pharmaceutical and therapeutic properties.

- Ibuprofen is a nonsteroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. Ibuprofen has pharmacologic actions similar to those of other prototypical NSAIA, which are thought to act through inhibition of prostaglandin synthesis. The half-life of Ibuprofen is 2-4 hours. It is used in the management of many inflammatory conditions.
- The increasing incidence of ulcerative colitis has been reported from western countries and other parts of the world. Even in India this disease is diagnosed to be more common. Though, there is need to study the disease and its complications from our country. Inflammatory bowel disease is an uncommon but important health problem. It is particularly likely to affect young people. The present investigation deals with development of effective and stable enteric coated matrix tablet of Ibuprofen for the effective treatment of inflammatory bowel diseases.

  - To formulate Ibuprofen matrix tablets and coated with enteric polymer.
  - To evaluate the formulated tablets as per requirements of IHS standards.
  - To evaluate the most satisfactory formulation.
  - To select the best formulation based on *in-vitro* studies for colon targeting.
  - To perform stability studies on the most satisfactory formulation.

2.2 PLAN OF WORK

The present work was carried out to formulate the colon targeted matrix tablets of Ibuprofen and to evaluate the various parameters. It was planned to carry out this work as outlined below.

- To carry out the Preformulation studies to maximize the chances in formulating an acceptable, safe, efficacious and stable product.

  a) Evaluation of API

  - Description
  - Solubility
  - Melting point
  - Particle size distribution
  - Loss on drying

  b) Drug excipient compatibility studies

  - Physical observation
  - FT-IR studies.

- Formulation of uncoated Ibuprofen tablets by direct compression method.
- Evaluation of the granules such as
  - Angle of repose
  - Bulk density
  - Tapped density
  - Compressibility index
  - Hausner's ratio
- Evaluation of physical parameters for compressed tablets.
  - Weight variation
  - Thickness
  - Hardness
  - Friability

- Disintegration
- Determination of drug content

- Coating of the formulated Ibuprofen tablets by using Eudragit FS 30D by pan coating method.
- Evaluation of the coated tablet.
- Evaluation of the most satisfactory formulation.
- *In-vitro* Drug Release Studies.
- To carry out the stability studies for the best formulation.

CHAPTER 3

REVIEW OF LITERATURE

3. REVIEW OF LITERATURE

Neha Singh Raghuvanshi *et al.*, (2014)[44] Formulated and evaluated matrix tablets of Prednisolone by wet granulation method using various proportions of Sterculia gum with Carbopol 934P and Sterculia gum with Ethyl cellulose at 1:1, 1:5 and 1:2 ratio. Coating was carried out by using 1:1 ratio of Eudragit L100 and Eudragit S100. All the preparation were evaluated for Pre compressional properties, Post compressional properties and *in-vitro* dissolution study in different pH buffer of 0.1N HCL , pH 7.4 and pH 6.8 in order to mimic GIT condition. All the parameters were found to be within the limits. Formulation F4 showed 85.46% at the end of 12 hrs and emerged as best formulation.

Sumit Kumar *et al.*, (2012)[45] Developed colon targeted matrix tablets of Naproxen to prolong the release for sustained effect. Different formulation (MT1 TO MT3) batches were made with the help of different polymers and their different proportions (Guar Gum, Xanthan Gum) with the help of Wet granulation techniques. The prepared matrix tablets were evaluated in terms of their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content and *in-vitro* drug release. All the parameters were found to be within the limits. From this study it concluded that the batch MT3 showed 77.99 % drug release then the other batches. The batch MT3 showed maximum prolonged release up to 12 hrs and concluded as best formulation.

Biresh Kumar Sarkar *et al.*, (2012)[46] Developed colon targeted matrix tablets of Flurbiprofen to prolonged the release for sustained effect. Different formulation (F1 TO F9) batches were made with the help of different polymers and their different proportions (Guar Gum, Eudragit RL, Eudragit RS) with the help of Wet granulation techniques. The prepared matrix tablets were evaluated in terms of their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content and *in-vitro* drug release. All the parameters were found to be within the limits. The batch F7 showed the maximum prolonged drug release 99.6% up to 12 hrs and concluded that the batch F7 as best formulation.

Sharma Madhu *et al.*, (2012)[47] Formulated and evaluated the sustained delayed release tablets of Mesalazine. The time and pH dependent drug delivery system, reduce the frequency of dose administeration, to prevent ulcerative colitis by developing sustained delayed release tablets of Mesalazine using combination of Eudragit S-100 and L-100 as enteric coating. The core tablets of Mesalazine were prepared using wet granulation containing a superdisintegrant. The aim of study was to develop colon specific drug delivery of Mesalazine sustained release matrix tablets for ulcerative colitis using HPMC K-4M and HPMC K-15M as a semisynthetic polymer. Effect of polymer concentration and superdisintegrant level was also investigated. The matrix tablets of Mesalazine are subjected to an *in-vitro* drug release study using simulated gastric fluid (0.1N HCl) for 2 hours, simulated intestinal fluid (pH 7.4) for 3 hours and simulated colonic fluid (pH 6.8) for 7 hours as dissolution fluid. The study showed that, lag time prior to drug release was highly affected by the coating. Colon drug delivery is advantageous in treatment of colonic disease and oral delivery of drugs that are unstable and susceptible to enzymatic degradation in upper GI tract. The disintegration data obtained from tablets demonstrated that disintegration data rate of studied tablets is dependent on: (i) The polymer used to coat the tablets (ii) pH of disintegration media. Results also demonstrated that combination of Eudragit S-100 and L-100 can be successfully used to coat tablets for colon targeted delivery of drug. Tablets were evaluated in terms of their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content and *in-vitro* drug release. All the parameters were found to be within the limits. Formulation F4 showed 90.25% at the end of 12 hrs and emerged as best formulation.

R.Prashanthi *et al., (*2014)[48] Developed the controlled release matrix tablets of Flurbiprofen by selecting different polymers like HPMC K100, Sodium Carboxy Methyl Cellulose, Xanthan gum and Guar gum. All the formulations were prepared by direct compression method using 12mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were showed good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F12 formulation that is with Guar Gum showed maximum percentage drug release 99.18 % in 12 hours. Hence it is

considered as optimized formulation. The retardation in the release of the drug from optimized formulation is may be due to the increase in the concentration of the polymer.

Lone Krishnakumar Devrao *et al.*, (2012)[49] Formulated and Evaluated the Matrix Tablet of Mesalazine with Hydroxypropylmethylcellulose Phthalate. In this study slow released matrix tablets of Mesalazine were prepared using pH sensitive polymer HPMC-P with six concentrations by wet granulation method. The granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausners ratio. The tablets were subjected to weight variation, hardness, friability and drug content test. Invitro release studies revealed that only one formulation, P3 qualified the first stage of release while all the formulations qualified the second stage of drug release except P4 which deviated slightly. The release profiles were affected by variable concentration of matrix forming polymer and hence, the release of Mesalazine retarded with increase in proportion of HPMC-P. As HPMC-P is a pH sensitive polymer with threshold value 5.8 because of this effectively prevented the escape of drug at acid stage but allowed considerable amounts to be released in buffer stage I. The prepared tablets were evaluated in terms of their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content and *in-vitro* drug release. All the parameters were found to be within the limits. Formulation P6 showed 99.32% at the end of 12 hrs and emerged as best formulation.

Rajeswari P. *et al.*, (2016)[50] Developed colon targeted drug delivery system by using Chitosan as a carrier for Mesalamine. Matrix tablets containing various excipients and Chitosan were prepared by wet granulation technique using different binder systems. The prepared tablets were evaluated for Hardness, Weight variation, Drug uniformity, Friability and *In-vitro* Drug release study. All the parameters were found to be within the limits. The final product is expected to have the advantage of being biodegradable and pH dependant. The matrix tablet containing Chitosan as a carrier and xanthum gum as binder was found to be suitable for targeting mesalamine for local action in the colon as compare to other matrix tablets containing different binders. Matrix tablets containing Chitosan released 99.99% of mesalamine in simulated colonic fluid. The stability study for prepared tablets at 40^{o}C/75% relative humidity for three months showed no significant change in *In-vitro* drug release pattern. The results of *in-vitro* study

indicate that matrix tablets containing Chitosan as carrier and xanthum gum as binder are most suitable to deliver the drug specifically in colonic region. The final formulation of mesalamine for colon-specific drug delivery gives pH, time and enzyme controlled release. Formulation F6 showed 99.29% at the end of 24 hrs and emerged as best formulation.

Prasanta kumar choudhury *et al.*, (2012)[51] Developed the matrix tablets of Ornidazole were prepared by wet granulation method using matrix forming natural polymers like Guar gum and Xanthan gum in combination with different proportions. The further effect of enteric coat on the matrix tablets for colon specific drug release was investigated. The Ornidazole optimized matrix formulation OM1 showed drug release around 32.37±0.33% in 2 hrs. So it was further enteric coated with 5% Eudragit S100 and coded as OME1 which showed 44.09±0.16% of drug release after 12 hrs. All formulations were subjected to Hardness test, Friability test, determination of uniform diameter and thickness, drug content for optimization and further evaluation. *In-vitro* dissolution studies indicated that the drug release in upper part of GIT from matrix tablets of Ornidazole can be prevented by enteric coating with pH sensitive polymer (Eudragit®S100), which releases the drug specifically in colonic region to achieve target delivery. All the parameters were found to be within the limits. Formulation OME1 showed 44.09% of drug release at the end of 12 hrs and emerged as best formulation.

Basavaraja *et al.*, (2015)[52] Formulated and evaluated the sustained release matrix tablets of Flurbiprofen. By using the natural and synthetic polymers. Flurbiprofen is NSAID drug used extensively in the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, Ankylosing Spondylitis, acute musculoskeletal disorders, low back pain and allied conditions. The natural polymers are Xanthan gum, Karaya gum, and synthetic polymers like HPMC K-100, Ethyl cellulose were utilized in the formulation of matrix tablets containing Flurbiprofen by wet granulation technique and evaluated for its *in-vitro* drug release. Natural polymer is hydrophilic in nature and rate controlling polymers. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, showed satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), *in-vitro* drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The *in-vitro*

release study of matrix tablets were carried out in pH 1.2 HCl for 2 hours and pH 7.4 phosphate buffer for the remaining 10 hours as dissolution medium. Among all the formulation, F12 showed 97.23% of drug which was better controlled release at the end of 12 hrs. It has been found that the optimized formulation F-12 containing 500 mg of ethyl cellulose better sustained effect for 12 hrs and emerged as best formulation.

B. Manjula *et al.*, (2016) [53] Formulated and evaluated the colon specific tablets of Ornidazole tablets were successfully prepared using enteric coated polymers eudragit, guar gum and HPMC k15m study of the preformulation charcteristics and FTIR studies indicates that there was no interaction between ornidazole and excipients used in the formulation. *In-vitro* release profiles of optimized form of F7 were found to showed delayed release pattern in a very customized manner which was very much required for the colon specific drug delivery. *In-vitro* release profiles of optimized formulation of ornidazole controlled release tablets (F-7) were found to be improvised and followed zero-order kinetics, hence the release of the drug from the dosage form was independent of concentration and followed Higuchi model, and hence release of drug from press coated tablet was by diffusion mechanism. The drug delivery system was designed to deliver the drug at such a time when it was needed nocturnal time. Formulation F7 showed 75.98% of drug release at the end of 10 hrs and emerged as best formulation.

L. Matsyagiri *et al.*, (2014)[54] Formulated and evaluated the colon specific drug release of Albendazole with the purpose of developing a release of drug at colon region for local action, which is very convenient for administration, without the problem of enzymatic degradation and effect of pH of upper part of GIT like stomach and small intestine. Colon specific matrix tablets of Albendazole were prepared using guar gum, xanthene gum and HPMC polymers as matrix. FTIR showed that there is no interaction between drug and excipients. *In-vitro* dissolution of prepared matrix tablets of Albendazole performed by using USP type II apparatus in pH 0.1N first 2 hrs and remaining three hours in phosphate buffer pH 7.4 phosphate buffer solutions. The tablets were evaluated for various parameters like thickness, drug content uniformity, weight variation, hardness, friability and *in-vitro* drug release, all were showed satisfactory results. It is concluded that colon specific drug release of Albendazole give all satisfactory results for

formulation F1-F9. Formulation F7 showed 87.02% of drug release at the end of 12 hrs and emerged as best formulation.

Patel Jayvadan K *et al.*, (2009)[55] Developed the colon targeted drug delivery system by using Chitosan as a carrier for Mesalamine. Matrix tablets containing various excipients and Chitosan were prepared by wet granulation technique using different binder systems. The prepared tablets were evaluated for Hardness, Weight variation, Drug uniformity, Friability and *In-vitro* Drug release study. The surface of the device of best formulation was coated with Eudragit S100 to ensure that the device was more pH dependent and trigger the drug release only at higher pH. The final product is expected to have the advantage of being biodegradable and pH dependant. The matrix tablet containing Chitosan as a carrier and Hydroxypropyl methyl cellulose as binder was found to be suitable for targeting mesalamine for local action in the colon as compare to other matrix tablets containing different binders. Matrix tablets containing Chitosan released 97-99% of mesalamine in simulated colonic fluid. The stability study for prepared tablets at 40oC/75% relative humidity for three months showed no significant change in *In-vitro* drug release pattern. The results of *in-vitro* study indicate that matrix tablets containing Chitosan as carrier and Hydroxypropyl methyl cellulose as binder are most suitable to deliver the drug specifically in colonic region. The final formulation of mesalamine for colonspecific drug delivery gives pH, time and enzyme controlled release. All the parameters were found to be within the limits. Formulation F9 showed 90.25% at the end of 12 hrs and emerged as best formulation.

Sam T Mathew *et al.*, (2016)[56] Formulated and evaluated the matrix tablets of albendazole containing various proportions (20%, 25%, 30% and 35%) of guar gum, xanthum gum and dextrin were prepared by direct compression technique using 10 mm concave punch. The prepared tablets were evaluated for hardness, friability, weightvariation, drug content uniformity and were subjected to *in-vitro* drug release with and without rat caecal content (4% w / v). All formulations (F1 - F12) which shows restricted drug release in stomach and small intestine and which shows more release in colonic environment. The drug release was independent of its concentration and the mechanism of drug release followed by super case-II transport. The accelerated stability studies revealed that there was no significant change in the colour, shape

and drug content. The formulation (F9) is most suitable to target colon without being released significantly in the stomach and small intestine, and also it may avoid systemic side effects in the gastrointestinal tract. All the parameters were found to be within the limits. Formulation F9 showed 94.25% at the end of 12 hrs and emerged as best formulation.

Shekhar singh *et al.*, (2013)[57] Developed the colon targeted matrix tablets of the drug Flurbiprofen. NSAIDS class of drug that is designed to for sustained effect. Different formulation (F1 TO F9) batches were made with the help of different polymers and their different proportions (Guar gum, Eudragit RL, Eudragit RS) with the help of Wet granulation technique. The prepared matrix tablets were evaluated in terms of their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content, *in-vitro* drug release. The *in-vitro* release study had been done into simulated gastric and intestinal fluid with a new method. From this study we concluded that the batch F7 showed good results then the other batches. The batch F7 showed maximum prolonged drug release 97.34% upto 12 hrs and emerged as best formulation.

K. Ramesh Reddy *et al.*, (2015)[58] Formulated the Prednisolone matrix tablets for colon targeting drug delivery system by using pectin and chitosan polymers. Prednisolon**e** is synthetic Glucocorticoids, a derivative of cortisol, which is used to treat a variety of inflammatory and auto-immune conditions. Colon targeted drug delivery is an active area of research for local diseases affecting the colon, as it improves the efficacy of therapeutics and enables localized treatment, which reduces systemic toxicity. Targeted delivery of therapeutics to the colon is particularly advantageous for the treatment of inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease. Prednisolone matrix tablets were prepared by wet granulation technique by using different polymers such as chitosan and pectin are sustained release polymers. Starch mucilage is a granulating agent .The matrix tablets were evaluated their compatibility studies by using FT-IR, micromeritics properties, post formulation characters, stability and *in-vitro* dissolution studies. The batch F2 showed maximum prolonged drug release 96.79% at the end of 12 hrs and emerged as best formulation.

G. Subba Rao *et al.*, (2013)[59] Formulated the controlled release tablet of Diltiazem hydrochloride for colon targeting tablets using gum kondagogu. The drug excipient interaction studies were carried out by FTIR, DSC, and XRD studies.The prepared matrixes showed controlled delivery for over 18hrs.Studies were also carried out in presence of 4% w/v RCC. *In-vitro* drug release studies showed that F6 released 92%, 94% in stimulated colonic fluid and 98% in stimulated colonic fluid in presence of rat cecal content in a controlled manner over a period of 18 hours. Formulation F6 was optimized and put for Stability studies. Stability studies revealed that matrix tablets were stable over a period of 6 months. All the formulation followed zero order release kinetics and fit into peppas model of drug release. The batch F6 showed maximum prolonged drug release 98.34% upto 12 hrs and emerged as best formulation.

Satinder Kakar *et. al,* (2014)[60] Developed the colon targeted drug delivery system by using Chitosan, Eudragit S 100 and Ethylcellulose and to compare the results obtained by three different carrier systems. Results obtained were fitted to different mathematical models to estimate which model fits best to the drug release. Wet granulation technique was employed for the preparation of prolonged release matrix tablets. Tablets containing chitosan as carrier system were found to show prolonged release in the colon. Kinetic models were applied among which Higuchi model suits best.

Prasanta Kumar Choudhury *et al.*, (2012)[61] Formulated the colon specific drug delivery of Ornidazole . The formulation of colon specific drug delivery system (CDDS) was designed such that the innermost part consists of an immediate release core tablet of Ornidazole which is then compression coated with a pH-independent hydrophilic polymer (Hydropropylmethyl cellulose-HPMC K4M). This is then coated with a pH-dependent methacrylic acid copolymer (Eudragit S100). The optimized concentration (coating level) of Eudragit S100 provides an enteric coat that protects the tablet from the hostile environment of stomach and is targeted to the colon. The coating thickness and core to coat ratio of HPMC were optimized to set a desired lag time in the intestine. The evaluation parameters and *in-vitro* drug release data attests that the developed CDDS can exhibit site-specific drug delivery to the colon. The batch F7 showed maximum prolonged drug release 98.34% upto 12 hrs and emerged as best formulation.

Magdum Sonali Vijaykumar *et al*., (2016)[62] Formulated and evaluated the colon targeted tablet by using various proportion of guar gum. Budesonide drug was selected for this research work. The Budesonide which is used for treating colonic diseases. The tablet was formulated by using Guar gum, Lactose Starch, Talc and Magnesium Strearate.The tablets were evaluated for thickness, hardness and friability and all this was found to be in within range. The *in-vitro* dissolution study was carried out by using different PH of phosphate buffer solution as 250 ml HCL buffer PH 1.2 for 2 hr., 250 ml phosphate buffer PH 6.8 for another 3hr.and finally250 ml PBS PH7.4 till the end of 12hr.The drug release of all the formulation was found to be within range of 92.23 to 98.38%.tablet was capable to release drug at colon and protect the tablet from acidic PH. The batch F3 showed maximum prolonged drug release 98.38% upto 24 hrs and emerged as best formulation.

Dr. T. Satyanarayana *et al*., (2017)[63] Formulated and Evaluated the Mesalazine colon targeted matrix tablets was done by using various polymers. To achieve pH independent drug release of Mesalazine, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F7 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 97.87% drug release. It followed first order kinetics mechanism. Stability studies was Performed no chemical changes was occurred

Srilakshmi N *et al*., (2015)[64] Formulated and Evaluated the Metronidazole enteric coated tablets for colon targeting .Colon specific drug delivery has gained importance for the delivery at colonic region by use of various drugs to treat both local and systemic diseases. Local diseases include Chron's disease, ulcerative colitis, colorectal cancer, amoebiasis etc. The active ingredient Metronidazole has to be delivered to the colon for effective action against trophozoites of *E. histolytica* and *Giradia lamblia*, wherein the respective trophozoites reside in

the lumen of caecum and large intestine and adhere to colonic mucus and epithelial layers. Formulating Metronidazole as conventional tablets give side effects which occur due to absorption of drug from upper part of GIT and the pharmacokinetic profile of Metronidazole indicates that the drug is completely absorbed in approximately 1 hr after a single dose. So, various synthetic hydrophilic polymers are used to control the drug delivery and target the drug to the intestine using enteric coated polymers. The present study aimed to formulate the core tablets using different polymers such as HPMC K 15M and HPMC K100M in different ratios and the core tablets were coated with an enteric polymer. The prepared tablets were evaluated for weight variation, hardness, friability, content uniformity and *in-vitro* drug release study first in 0.1N HCl followed by in pH 7.4 phosphate buffer. Formulation F12 showed good targeted site controlled drug delivery, as it showed 96% drug release for 24 hrs and emerged as best formulation.

.**J. R. Jadhav *et al*., (2012)**[65] Formulated and evaluated the colonic compression coated tablet of budesonide. The *in-vitro* performance of compress coated tablet of Budesonide. A novel colon targeted tablet formulation was developed by press coating of Budesonide with guar gum and Eudragit S-100 as barrier layer. The entire device was enteric coated so that variability in gastric emptying time can be overcome and a colon specific release can be achieved. Different ratios of polymers were selected to achieve suitable lag time for the treatment of Crohn's disease and ulcerative colitis. *In-vitro* release studies for prepared tablets were carried out for 2 h in 1.2 pH phosphate buffer, 3 h in pH 6.8 phosphate buffer and 6 h in simulated colonic fluid. In vitro studies revealed that the tablet coated with guar gum and Eudragit S-100 have limited drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment. Colon specific release has been achieved from tablet of F5 formulation which not given release in stomach and small intestine and about 98.87% drug release in the colon. Formulation F5 showed good targeted site controlled drug delivery, as it showed 98.87% drug release for 24 hrs and emerged as best formulation.

CHAPTER 4

MATERIALS AND METHODS

LIST OF CHEMICALS USED

4.1. LIST OF CHEMICALS USED

Table No: 2

S.No	Name of Ingredients	Category	Manufacturer/Suppliers
1	Ibuprofen	Drug	Shasun chemicals, Chennai.
2	Eudragit S100	polymer	Vikram Thermo (India) LTD Ahmedabad.
3	Ethyl cellulose	polymer	Jalan cellulose. Co, India.
4	Lactose (DCL 21)	Diluent	Cabot sanmar LTD, Chennai.
5	Talc	Lubricant	Abishek organics, Mumbai.
6	Magnesium stearate	Lubricant	Amishi Drugs and Chemicals, Gujarat.
7	Eudragit FS 30D	Enteric coating flim former	Vikram Thermo (India) LTD Ahmedabad.
8	Tri Ethyl Citrate	Plasticizer	Chemtrec –International LTD
9	Purified talc	Anti tacking agent	Abishek organics, Mumbai.
10	Purified water	Vechicle	Fourrts india, Chennai

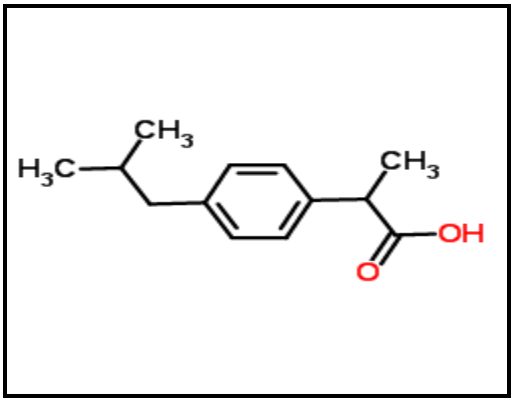
DRUG PROFILE

4.2. DRUG PROFILE

IBUPROFEN

GENERAL DESCRIPTION [66, 67, 68]

Structural formula:



Chemical name : (RS)-2-(4-(2-methylpropyl) phenyl) propanoic acid.

Molecular formula : $C_{13}H_{18}O_2$

Molecular weight : 206.29 g/mol

Therapeutic category : Anti-inflammatory, analgesic, prostaglandin synthesis inhibitor.

Description : A white or almost white, crystalline powder or colourless crystals Odourless.

Melting point : 75.0^0 C to 77.5^0 C

Boiling point : 157 °C

Dose : 200mg to 1.2g daily, in divided doses, after food.

Storage : Stored at room temperature, between 15-30^0C.

SOLUBILITY:

Soluble in ethanol,chloroform,ether,acetone,aqueous solutions of alkalihydroxide and carbonate, dichloromethane, methanol,ethyl acetate.Insoluble in water**.**

MECHANISM OF ACTION[69, 70]:

Ibuprofen, it is a Non Steroidal Anti-inflammatory Drug (NSAID) coming under the class of propionic acid derivatives. It is a potent analgesic, antipyretic and anti-inflammatory drug. It has poor uricosuric effect. It is a potent prostaglandin synthesis inhibitor like aspirin. It has antiplatelet action.

The main action of this drug is inhibition of arachidonate cyclo-oxygenase. Ibuprofen,which binds reversibly to the enzyme competing with the natural substrate (arachidonic acid),has a rapid, reversible competitive inhibition. This action is manifested by the propionic acid NSAIDs.

PHARMACODYNAMICS[71]:

Analgesic, Anti-inflammatory, and Antipyretic actions. Ibuprofen inhibits prostaglandin synthesis.

PHARMACOKINETICS[72]:

All propionic acid derivatives enter brain, synovial fluid, and cross placenta.

- Absorption **:** Part of oral dose is absorbed from gastrointestinal tract.
- Distribution **:** Highly protein-bound.
- Metabolism **:** Undergoes biotransformation in the liver.
- Excretion **:** Excreted mainly in urine, and some in bile.

Oral absorption **:** 98-99%

Onset of action **:** 30-60 min

Duration **:** 4-6 hrs

Plasma half life **:** 2-4 hrs

Plasma protein bound **:** 99%

Excretion **:** 90%

Metabolites **:** Hydroxylated and carboxylated compound.

CONTRAINDICATIONS AND PRECAUTIONS:

Contraindicated in patient with hypersensitivity to drug or in those who have the syndrome of nasal polyps, angioedema and bronchospastic reaction to aspirin or other Non Steroidal Anti inflammatory Drugs (NSAIDs) Use cautiously in patients with impaired renal or hepatic function, gastrointestinal disorders, peptic ulcer disease, cardiac decompensation, hypertension or coagulation defects. Chewable tablets conain aspartame, use cautiously in patients with phenylketonuria. Ibuprofen is contraindicated during the last trimester of pregnancy because it may cause problems with the fetus, or complication during delivery.

ADVERSE REACTIONS[73]:

Central nervous : Headache, Dizziness, Nervousness, Aseptic meningitis.

Cardiovascular : Peripheral edema, fluid retention, edema.

Gastrointestinal : Epigastric distress, nausea, occult blood loss, peptic ulceration.

Genitourinary : Acute renal failure, azotemia, cystitis, hematuria.

Hematologic : Prolonged bleeding time, anemia, neutropenia, pancytopenia, Thrombocytopenia, Aplastic anemia, Leucopenia, agranulocytosis.

Hepatic : Elevated enzymes.

Respiratory : Bronchospasm.

Skin : Pruritus, rash, urticaria, Stevens – Johnson syndrome.

DRUG INTERACTIONS:

With Acetyl CoA Enzyme inhibitors : Reduced response when used together; may result in Acute reduction in renal function.

With Antacids **:** May decrease the absorption of Ibuprofen.

Aspirin **:** May decrease the bioavailability of Ibuprofen.

Coumarin derivatives,

Nifedipine,phenytoin,verapamil **:** Toxicity may occur with concurrent us Avoid use together.

Diuretics, antihypertensives **:** Concurrent use may decrease effectiveness of these drugs; Diuretics may increase nephrotoxicity.

Other anti-inflammatory agents **:** Increased nephrotoxicity may occur.

Insulin or oral antidiabetic agents **:** May potentiate hypoglycemic effects.

Lithium, Methotrexate **:** Decreased renal clearance of these drugs.

USES[74]:

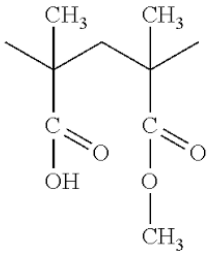
- As an analgesic in painful conditions.
- In fever.
- In gout.
- For soft tissue injuries, fractures, following tooth extraction.
- To relieve postoperative pain, dysmenorrhoea and osteoarthritis.

EXCIPIENTS PROFILE

4.3 EXCIPIENTS PROFILE[75]

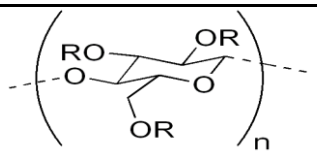
EUDRAGIT S100

Table No: 3

S.NO	PROPERTIES	DESCRIPTION
1	Synonyms	Polymeric methacrylates
2	Chemical name	Poly (methacrylic acid-co-methyl methacrylate) 1:2
3	Structural formula	
4	Molecular weight	approx. 125,000 g/mol
5	Melting point	160^0C
6	Description	It occurs as a fine white free flowing powder
7	Solubility	Soluble in acetone and alcohols and 1N NaOH. EUDRAGIT S 100 is practically insoluble in ethyl acetate, methylene chloride, petroleum ether and water.
8	Functional category	Film former, Tablet binder, Tablet diluents
10	Application	Used as enteric coating agents because they are resistant to gastric fluid
11	Stability	Dry powder polymer forms are stable at temperature less than 30^0C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substances and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 300C
12	Incompatibilities	Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent.

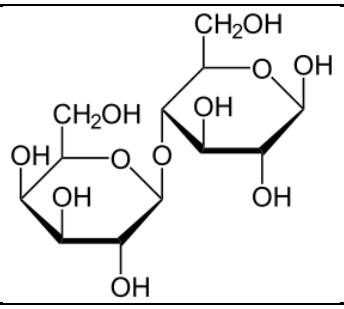
ETHYL CELLULOSE

Table No: 4

S.NO	PROPERTIES	DESCRIPTION
1	Synonyms	Aquacoat, Ethocel 7cP,ethyl cellulose, Surelease
2	Chemical name	Cellulose ethyl ether
3	Molecular formula	$C_{20}H_{38}O_{11}$
4	Molecular structure	 R = H or CH_2CH_3
5	Molecular weight	454.513g/mol
6	Melting point	240-255
7	Description	Free- flowing, white to light tan- colored powder
8	Solubility	Practically insoluble in water in glycerol and in propylene glycol, but soluble in varying proportions in certain organic solvents depending upon the ethoxyl content.
9	Functional category	Coating agent, Flavoring agent, Tablet binder, Tablet filler
10	Application	The main use of Ethyl cellulose in oral formulation is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coating is used to modify the release of drug and to mask an unpleasant taste or to improve the stability of a formulation.
11	Incompatibilities	Incompatible with paraffin wax and microcrystalline wax

LACTOSE DCL 21

Table No: 5

S.NO	PROPERTIES	DESCRIPTION
1	Synonyms	Lactose Anhydrous NF DCL-21, Pharmatose DCL21, Lactosum.
2	Chemical name	Alpha- lactose, Anhydrous lactose.
3	Molecular formula	$C_{12}H_{22}0_{11}$
4	Molecular structure	
4	Molecular weight	342.30g/mol
5	Melting point	202.8^0C
6	Description	White to off white crystalline particles or powder, odourless and slightly sweet tasting.
7	Solubility	Soluble in water, Sparingly soluble in ethanol.
8	Functional category	Used in the direct compression of tablets (tablet binder)
9	Application	Anhydrous lactose is widely used in direct compression tableting application and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture sensitive drugs due to its low moisture content.
10	Incompatibilities	Lactose is incompatible with strong oxidizers.
11	Stability	Anhydrous lactose should be stored in a well closed container in a cool, dry place.

PURIFIED TALC

Table No: 6

S.NO	PROPERTIES	DESCRIPTION
1	Synonyms	Altalc; E553; hydrous magnesium calcium silicate; Luzenac Pharma; Magsilosmanthus; Magsil Star; Powdered talc; Purified French chalk; soapstone; Steatite; Superior.
2	Chemical name	Talc
3	Molecular formula	$Mg_6 (Si_2O_5)_4(OH)_4$
4	Molecular weight	379.3 g/mol
5	Melting point	93^0 C
6	Description	Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.
7	Solubility	Practically insoluble in dilute acids and alkalis, organic solvents and water.
8	Functional category	Anti-caking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant
9	Application	It is widely used as a dissolution retardant in the development of controlled release products. Talc is also used as lubricant in tablet formulations, coating for pellets and as an adsorbent in topical preparations. Talc is used as a dusting powder and also used to clarify liquids and it is mainly used in food and cosmetic products as a lubricant.
10	Incompatibilities	Incompatible with quaternary ammonium compounds.

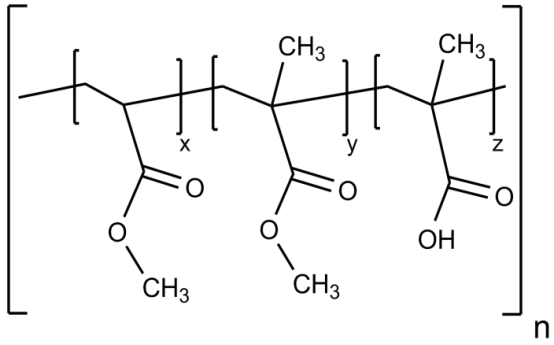
MAGNESIUM STEARATE

Table No: 7

S.NO	PROPERTIES	DESCRIPTION
1	Synonyms	Magnesium octadecanoate, stearic acid, magnesium salt.
2	Chemical name	Octadecanoate stearic acid magnesium salt
3	Molecular structure	$[CH_3 (CH_2)_{16} COO]_2 Mg$
4	Molecular weight	591.27g/mol
5	Melting point	88^0C
6	Description	It occurs as a fine, white precipitated or milled impalpable powder with a faint odour and a characteristic taste.
7	Solubility	Practically insoluble in ethanol, ether and water, slightly soluble in warm benzene and warm ethanol (95 %).
8	Functional category	Lubricant.
10	Application	It is widely used in cosmetics, food, pharmaceutical formulations. It is primarily used as lubricant in capsule and tablet manufacture at concentrations between 0.2-5.0 percent.
11	Stability	It is stable and should be stored in a well closed container in a cool and dry place.
12	Incompatibilities	It is incompatible with strong acids, alkalis and iron.

EUDRAGIT FS 30D

Table No: 8

S.NO	PROPERTIES	DESCRIPTION
1.	Chemical name	Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid)
2.	Molecular structure	
3.	Molecular weight	280000 g/mol
4.	Description	Milky-white liquid of low viscosity with a faint characteristic odour.
5.	Solubility	The dispersion is miscible with water in any proportion, the milky-white appearance being retained. A clear or slightly cloudy, viscous solution is obtained by mixing 1 part Eudragit FS 30 D with 5 parts acetone. The same results are obtained by mixing with ethanol or isopropyl alcohol; initially, the polymer is precipitated, but then dissolves again in the excess organic solvent. A clear or slightly cloudy liquid is obtained by mixing 1 part Eudragit FS 30 D with 2 parts 1 N sodium hydroxide.
6.	Application	Used as enteric coating agents because they are resistant to gastric fluid.

LIST OF EQUIPMENTS USED

4.4. LIST OF EQUIPMENTS USED

Table No: 9

S. No	Name of the Equipment	Manufacturer
1.	Weighing balance	Shimadzu
2.	Bulk density apparatus	Thermonik
3.	Compression machine (8 station)	Accura
4.	Coating pan	Electro lab
5.	Hardness tester	Thermonik
6.	Thickness tester	Mitutoyo corps, Japan
7.	Friability tester	Electro lab
8.	Disintegration apparatus	Electro lab
9.	Dissolution apparatus	Lab india
10.	I.R moisture balance	Citzen
11.	pH analyzer	Lab india
12.	FTIR Spectrophotometer 8300	Perkin Elmer
13.	U.V spectrophotometer	Shimadzu
14.	Ultra Sonicater	Lab man scientific instrument
15.	Electromagnetic Sieve Shaker	Electro pharma

METHODOLOGY

4.5 METHODOLOGY

4.5.1. PREFORMULATION STUDIES: [76]

Preformulation is the first step in the rational development of dosage form of a substance and is defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients. This initial learning phase is known as preformulation.

The basic purpose of the preformulation activity is to provide a rational basis for the formulation approaches, to minimize the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance. The first step in any formulation activity is careful consideration of a complete physicochemical profile of the active ingredients available, prior to initiating a formulation development activity.

CONTENTS OF PREFORMULATION STUDIES:

- Background – Compound chemical name, chemical structure, solvent of recrystallization, purity, therapeutic category.
- Organoleptic properties – Appearance, colour and odour.
- Microscopic examination – Crystal habit, crystal shape and size.
- Physical properties – Density, particle size, surface area, flow properties, hygroscopicity.
- Solvent properties – pH of solution, solubility and dissolution rate, drug excipient compatibility study.

IMPORTANT PARAMETERS EVALUATED DURING PREFORMULATION STUDIES:

1. **Evaluation of API**

The Evaluation of Ibuprofen was done according to IP. Following are some of the important parameters evaluated during preformulation studies and results are tabulated in ***Table No: 22***

A. Description

It is the initial evaluation during preformulation studies which assess the colour of the substance. This was only a descriptive test.

B. Solubility

Aqueous solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy.

SOLUBILITY SPECIFICATIONS

Table No: 10

Descriptive terms	Approximate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	More than 10,000

C. Melting point

The temperature at which the first particle of the substance completely melts is regarded as melting point of the substance. The temperature at which the first particle start to melt and last particle completely melts is regarded as melting range. Melting point of Ibuprofen was conducted as per monograph.

D. Loss on drying

The loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. Loss on drying of Ibuprofen was measured by using moisture balance. Weigh approximately 2gm of Ibuprofen and placed into a plate of moisture balance. Set the temperature to 45°C. Measure the moisture content of drug in percentage.

E. Flow Properties (Angle of Repose) [77]

Angle of repose is defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane. The angle of repose of the powder or granules was determined by fixed funnel method. To assess the flow property of the powder granules, the height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder or granules above a paper that was placed on a flat horizontal surface. Accurately weighed powder blend was taken in a beaker. It was allowed to flow through the funnel freely on the surface of the paper to form a cone shaped pile. The diameter of the cone (d) and the height (h) of the pile was noted. From the diameter, radius (r) was calculated. The angle of repose (θ) was calculated using the following formula. The results were tabulated in ***Table No: 23.***

$$\Theta = \tan^{-1}(h/r)$$

ANGLE OF REPOSE AS AN INDICATION OF POWDER FLOW PROPERTY

Table No: 11

Flow properties	Angle of repose (degree)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Extremely poor	>66

I. Bulk density

Bulk density is a characteristic of a powder rather than individual particles and is given by the mass M, of the powder occupying a known volume, V_o. It is expressed in g/ml. An accurately weighed quantity of granules was transferred into a 50 ml measuring cylinder with

the aid of the funnel. The unsettled apparent volume, to the nearest graduated unit occupied by the granules was measured. Bulk density was determined using the formula. [78] The results were tabulated in ***Table No: 24.***

$$\rho_{bulk} = m/V_o$$

Where,

ρ_{bulk} = Bulk density;

m = Mass of the blend

V_o = Untapped Volume

J. Tapped density:

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken until little further volume change is observed. The measuring cylinder containing a weighed quantity of granules (after measurement of bulk density) was subjected to 500 taps in tapped density tester (Electro Lab USP II). The tapped density was calculated by using the formula. The results were tabulated in ***Table No: 24.***

$$\rho_t = m/V_t$$

Where,

ρ_t = Tapped density;

m = Mass of the granules

V_t = Final tapped volume.

4.5.2 MEASUREMENT OF POWDER COMPRESSIBILITY

- **Carr's compressibility index:**

Compressibility index are a measure of the tendency for arch formation and the ease with which the arches will fail. ***Table No: 12*** show the relationship between compressibility index and flowability. The results were tabulated in ***Table No: 25***. It is calculated by using the formula.[79]

$$\mathbf{CI = \rho_t - \rho_{bulk} / \rho_t \times 100}$$

Where,

CI = Compressibility index

ρ_{bulk} = Bulk density

ρ_t = Tapped density

CARR'S COMPRESSIBILITY INDEX:

Table No: 12

S. No.	Compressibility index (%)	Flow characters
1	< 10	Excellent
2	11-15	Good
3	16-20	Fair
4	21-25	Passable
5	26-31	Poor
6	32-37	Very poor
7	>38	Extremely poor

- **Hausner's ratio:**

Hausner found that the ratio ρ_t / ρ_{bulk} was related to interparticle friction and, as such could be used to predict powder flow properties. He showed that powders with low interparticle friction, such as coarse spheres, had ratios of approximately 1.2; whereas more cohesive, less free flowing powders such as flakes have values greater than 1.6. ***Table No: 13*** shows the flow characters and corresponding Hausner's ratio. The results were tabulated in ***Table No: 25***. It is calculated using the formula. [80]

$$\mathbf{Hausner's\ Ratio = \rho_t / \rho_{bulk}}$$

Where,

ρ_{bulk} = Bulk density

ρ_t = Tapped density

HAUSNER'S RATIO AS AN INDICATION OF POWDER FLOW

Table No: 13

S. No.	Hausner's ratio	Type of flow
1	1.0 –1.11	Excellent
2	1.12 – 1.18	Good
3	1.19 – 1.25	Fair
4	1.26 – 1.34	Passable
5	1.35 – 1.45	Poor
6	1.46 - 1.59	Very poor
7	>1.60	Extremely poor

- **Particle Size Analysis**

In case of tablets, size influences the flow and the mixing efficiency of powders and granules. Size can also be a factor in stability. Fine materials are relatively more open to attack from atmospheric oxygen, the humidity and interacting excipients than are coarse materials.

Particle size distribution of the drug was estimated by sieving method. The sieves are stacked on top of one another in ascending degrees of coarseness. The test powder, for example 10gm, was placed on the top sieve. The nest of sieves was subjected to a standard period of agitation. The weight of material retained on each sieve was accurately determined. Percentage of powder retained on each sieve was calculated by using the following formula. The results were tabulated in ***Table No: 26***.

$$\text{Percentage retained} = \frac{\text{Mass retained on each seive}}{\text{Total weight}} \times 100$$

CLASSIFICATION OF SAMPLE BASED ON THE PERCENTAGE OF SAMPLE RETAINED OR PASSED ON TEST SIEVES

Table No.14

S. No.	Nature of sample	Result of determination
1	Coarse powder	NLT 95% of the sample mass pass through #14 and NMT 40% pass through #36
2	Moderately coarse powder	NLT 95% of the sample mass pass through #25 and NMT 40% pass through #60
3	Moderately fine powder	NLT 95% of the sample mass pass through #36 and NMT 40% pass through #100
4	Fine powder	NLT 95% of the sample mass pass through #100 and NMT 40% pass through #150
5	Very fine powder	NLT 95% of the sample mass pass through #150 and NMT 40% pass through #200
6	Super fine powder	NLT 90% by number of particles are less than 10µm

2. DRUG-EXCIPIENT COMPATIBILITY STUDIES

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation scientist must generate the needed information.

A. Physical observation:

Active ingredient was mixed well with all excipients in binary ratio and small portion of this mixed powder was placed in a 2ml of cleaned and dried vial. This vial was kept for observation in stability chamber at $40^{o}C \pm 2^{o}C$ / 75 ± 5% RH. Mixtures were also placed at $2^{o}C$ -$8^{o}C$, $50^{o}C$ and room temperature (Control). Physical observation has been carried out visually at the initial stage, after 15 days and after 1 month at $40^{o}C \pm 2^{o}C$ / 75 ± 5% RH. The results were tabulated in ***Table No: 27.***

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Table No: 15

S. No	Drug and excipients	Parameter
1	Ibuprofen	Colour change
2	Ibuprofen + Excipients	Colour change

B. Chemical compatibility studies by FT- IR:

Physical compatibility studies were assured by FT-IR studies. The pure drug sample, drug-excipient mixtures of the formulation were chosen for the study. The FT-IR spectra's of the above samples were studied after a period of 30 days from preparation of the mixtures, to facilitate prompt detection of incompatibility. The spectra's were obtained by preparing Potassium bromide pellets under dry condition by using pellet press.

The spectra of the pure drug sample and that of the drug-excipient mixtures were compared to check the incompatibility problems. If there are no changes in peaks of mixture when compared to pure drug, it indicates the absence of chemical interaction. The FT-IR spectra's were as shown in **Figure No: 9, 10.**

4.5.3 PREPARATION OF GRANULES FOR COMPRESSION

Matrix tablet of Ibuprofen was prepared by direct compression method. All tablet ingredients was accurately weighed as mentioned in ***Table No. 16***. The average weight of each uncoated tablet was 450 mg.

Formulation of colon targeted matrix tablet of Ibuprofen.

The method used in the formulation of colon targeted matrix tablet of Ibuprofen was direct compression method .All the batch formulations in these studies are formulated by direct compression method.

- **Weighing:**

  A required quantity of raw materials was weighed accurately.

- **Sifting:**

  The Ibuprofen, eudragit S100 and ethyl cellulose were sifted using 60 # mesh. Lactose (DCL 21) sifted through 40 # mesh.

- **Mixing:**

  The sifted powders were mixed in polythene bag for ten minutes.

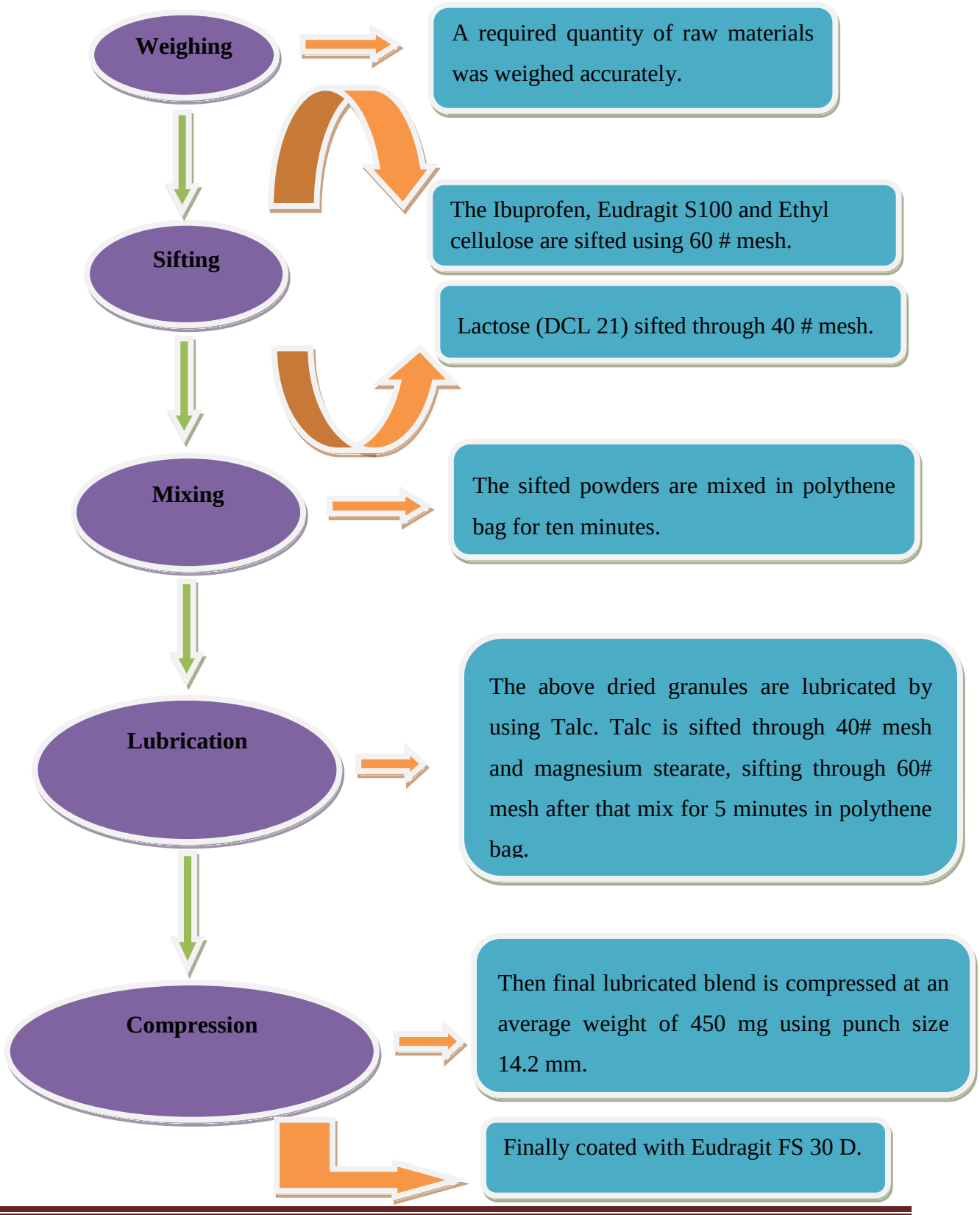
- **Lubrication:**

  The above dried granules were lubricated by using Talc. Talc is sifted through 40# mesh and magnesium stearate, sifting through 60# mesh after that mixed for 5 minutes in polythene bag.

- **Compression:**

  Then final lubricated blend was compressed at an average weight of 450 mg using punch size 14.2 mm.

FORMULATION FLOWCHART OF IBUPROFEN MATRIX TABLETS BY DIRECT COMPRESSION METHOD



FORMULATION TRIAL BATCHES

Table No: 16

S. No	INGREDIENTS	QUANTITY OF INGRIDIENTS (mg/tab)					
		F1	F2	F3	F4	F5	F6
1	Ibuprofen	250	250	250	250	250	250
2	Eudragit S-100	80	60	50	35	20	14
3	Ethyl cellulose	60	55	40	25	15	10
4	Lactose (DCL 21)	50	75	100	130	154	165
5	Talc	5	5	5	5	5	5
6	Magnesium stearate	5	5	5	5	6	6
Total weight (mg)		450	450	450	450	450	450

PERCENTAGE OF INGREDIENTS USED IN TRIAL BATCH FORMULATIONS

Table No: 17

S. No	INGRIDIENTS	QUANTITY OF INGRIDIENTS (%/tab)					
		F1	F2	F3	F4	F5	F6
1	Ibuprofen	55.55	55.55	55.55	55.55	55.55	55.55
2	Eudragit S-100	17.77	13.33	11.11	7.77	4.44	3.11
3	Ethyl cellulose	13.33	12.22	8.88	5.55	3.33	2.22
4	Lactose (DCL 21)	11.11	16.66	22.22	28.88	34.22	36.66
5	Talc	1.11	1.11	1.11	1.11	1.11	1.11
6	Magnesium stearate	1.11	1.11	1.11	1.11	1.33	1.33

4.5.4 COATING FORMULA:

Composition of Ingredient for Enteric Coating

6% coating has been given for all the formulations to protect the drug from acidic environment.

Table No: 18

S. No	Ingredients	Quantity/1000 Tablet (gm)
1	Eudragit FS 30 D	125
2	Triethyl citrate	1.875
3	Talc	18.75
4	Purified water	120

Preparation of Enteric Coating solution:

A required quantity of Eudragit FS 30 D was weighed accurately and stirred. Mean while Triethylcitrate was added to it, purified talc were triturated separately in a motar. And added to the solution and stirred. Finally the volume were make up to required quantity with purified water**.** Filtered the above solution with #100 mesh.

Weight built up calculation for enteric coating: [6 %]

450 x 6 % (6 gm ⟶ 100ml) 0.06 =27

450 + 27 = 477

The weight of enteric coated tablet = 477mg.

Coating Parameters

Operation Condition for Enteric Coating Process
Table No: 19

Specifications	Enteric coating range
Pan diameter	12
Speed of pan revolution	10-12 rpm
Distance of spray gun	5-6
Spray nozzle diameter	1.2 mm
Spray rate	1.5 -2.0 ml /min
Dry air temperature	50 ± 5^0C / 30 mins
Coating time	4 hours
Bed temperature	30-40^{0}C

4.5.5 EVALUATION OF POWDER BLEND

The powder blends were evaluated for the following parameters before compression into tablets.

1. Angle of repose
2. Bulk density
3. Tapped density
4. Compressibility index and Hausner's ratio.
5. Moisture content.

These procedures are discussed earlier in preformulation studies. The results were tabulated in ***Table No: 30.***

4.5.6 EVALUATION OF POST-COMPRESSION PARAMETERS:

The compressed tablets were evaluated for the following parameters.

General appearance

The tablets should be free from cracks, depression, pinholes etc. the color and polish of the tablets should be uniform on whole surface. The surface of the tablets should be smooth. The results were tabulated in ***Table No: 31.***

Hardness:

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging, and shipping. Tablet hardness has been defined as, the force required to break a tablet in a diametric compression test[81].Tablet hardness of all the formulations was measured using a Monsanto hardness tester.

Thickness:

Tablet thickness is an important parameter to be controlled to facilitate packaging. Tablet thickness, at constant compressive load, varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed; whereas at constant die fill, thickness varies with variations in compressive load. Tablet thickness must be controlled within a ±5% variation of a standard value. Any variation within a particular lot should not be apparent to the unaided eye of the consumer[80]. Thickness of all the formulations was measured using a digital vernier 76 tandar.

Friability:

Friability is a measure of the resistance of the tablet to abrasion. Tablets are generally subjected to a 76 standardized level of abrasion for a given time and the friability is expressed as a % weight loss. The measure is useful to determine the ability of the tablet to withstand abrasion during handling, coating, packing and transport. The laboratory friability tester is known as the Roche friabilator. This device subjects the tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that rotates at 25 rpm, dropping the tablets form a height of 6

inches with each revolution. Twenty tablets were weighed accurately and placed in the friabilator and was operated for 100 revolutions or 4 minutes. The tablets were then de dusted and weighed. The weight loss of 0.5 to 1% is considered as acceptable limits for conventional uncoated tablets. The weight loss was calculated using the formula.[82]

$$\text{Friability, F (\%)} = \frac{\text{Weight loss}}{\text{Initial weight}} \times 100$$

Disintegration Test:

USP disintegration test specifies that one tablet is added to each of the six tubes in the USP disintegration apparatus. The apparatus is operated without disks, using simulated gastric fluid (pH 1.2) at 37^0C for 2 hrs. The tablets are then removed and must show no evidence of disintegration, cracking or softening. Disks are then added and the apparatus is operated using simulated intestinal fluid (pH 7.4) at 37^0C for a period of time limit specified in the monograph. The product passes the test if all tablets are disintegrated.

Weight Variation Test:

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in and none deviate by more than twice the percentage.[83]

$$\text{Percentage deviation} = \frac{\text{Weight of tablet (mg)} - \text{Average weight of tablets(mg)}}{\text{Average weight of tablets}} \times 100$$

PERCENTAGE DEVIATION FOR WEIGHT VARIATION TEST

Table No: 20

S. No	Average weight of tablet(mg)	Percentage deviation
1	80 mg or less	± 10.0
2	More than 80 mg but less than 250 mg	± 7.5
3	250 mg or more	± 5.0

4.5.7 *IN-VITRO* DISSOLUTION STUDIES:

The release rate of Ibuprofen from tablets were determined using USP Dissolution Testing Apparatus 2 (paddle method).The test was performed using 900ml of 0.1N HCL at $37^0 \pm 0.5^0$C and 100 rpm for first 2 hrs. Then replaced with 7.4 pH phosphate buffer and continued for 24 hrs. A liquot volume of 5ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. The drug release is determined from the absorbance of the sample and standard. The results were tabulated in ***Table No: 34.***

Dissolution media Preparation:

- **Preparation of 0.1N HCl -** 8.5 ml of concentrated HCl was added to 1000 ml of purified water and the pH is 1.2.
- **Preparation of pH 7.4 phosphate buffer-** Dissolved 6.8g of potassium Dihydrogen phosphate in 1000 ml of purified water and adjusted the pH to 7.4 by using 0.1 N sodium hydroxide solution.

TEST A

Dissolution at Acid stage medium:

- Dissolution Medium: 900 ml of 0.1 N HCL
- Apparatus: USP Type II (Paddle)
- Rotation: 100 rpm
- Duration: 2 hours
- Temperature: 37˚C ± 0.5˚C

Standard Preparation

Weigh accurately about 27.0 mg of Ibuprofen working standard in to 100ml volumetric flask, add 50ml of methanol, shake for 5 minutes and make up to volume with methanol. Pipette out 10ml of the solution in to 100ml volumetric flask and make up to volume with dissolution medium. Further dilute 5ml of this solution to 10ml volumetric flask and make up to volume with dissolution medium.

Test preparation:

Withdraw 20ml of sample from each bowl and filter. Measure the absorbance of both standard and Test preparation at 222 nm using dissolution medium as blank and calculate the content of Ibuprofen per tablet.

Calculation:

$$\frac{Sample\ absorbance}{Standard\ absorbance} \times \frac{weight\ of\ standard}{100} \times \frac{10}{100} \times \frac{5}{10} \times \frac{900}{1} \times \frac{1}{100} \times \frac{purity\ of\ standard}{label\ claim} \times 100$$

TEST B

Dissolution at Buffer stage medium:

After filtering the dissolution medium for test A, drain the solution slowly without losing the tablet. Transfer the phosphate buffer medium to the bowl.

- Dissolution Medium: 900 ml of 7.4 phosphate buffer
- Apparatus: USP Type II (Paddle)
- Rotation: 100rpm
- Duration: 22 hrs.
- Sampling time: 5, 8, 12, 16, 20, 24 hrs
- Temperature: 37˚C ± 0.5˚C

Standard preparation

Weigh accurately about 27.0 mg of Ibuprofen working standard in to 100ml volumetric flask, add 50ml of methanol, shake for 5 minutes and make up to volume with methanol. Pipette out 10ml of the solution in to 100ml volumetric flask and make up to volume with dissolution medium. Further dilute 5ml of this solution to 10ml volumetric flask and make up to volume with dissolution medium.

Test preparation

Withdraw 10ml of test sample from the individual bowl at the end of 5^{th}hr and filter. Measure the absorbance and calculate the content of Ibuprofen as indicated in test A. Withdraw 10ml of test sample from the individual bowl at the end of 8^{th}hr, 12^{th}hr, 16^{th}hr, 20^{th}hr and 24^{th}hr and filter. Replace the bowl each time with buffer after withdrawal of the sample. Pipette out 1ml

of the filtrate and dilute to 20ml with the dissolution medium. Measure the absorbance of both standard and sample at 222 nm using dissolution medium as blank and calculate the content of Ibuprofen.

Calculation:

$$\frac{Sample\ absorbance}{Standard\ absorbance} \times \frac{weight\ of\ standard}{100} \times \frac{10}{100} \times \frac{5}{10} \times \frac{900}{1} \times \frac{20}{1} \times \frac{1}{100} \times \frac{purity\ of\ standard}{label\ claim} \times 100$$

4.5.8 ASSAY (By UV method)

Preparation of standard solution

Weigh accurately 100.0 mg of Ibuprofen working standard in a clean, 100 ml volumetric flask and 10ml of Acetonitrile. Shake well to dissolve and make up the volume to 100ml with phosphate buffer. Mix well and dilute 5ml with of this solution to 50ml with Phosphate buffer. Further dilute 5ml of the resulting solution to 50ml with phosphate buffer.

Preparation of sample solution

Weigh accurately about 190 mg of crushed tablet powder in a clean, 200 ml volumetric flask and add add 10ml of acetonitrile. Shake well and make up the volume to 200 ml with Phosphate buffer. And dilute 5ml with of this solution to 50ml with Phosphate buffer. Further dilute 5ml of the resulting solution to 25ml with phosphate buffer

Procedure

Measure the absorbance of both the standard and sample preparation at 222 nm using Phosphate buffer as blank. Assay was calculated from the following formula.

Calculation:

$$Drug\ content = \frac{Sample\ absorbance}{Standard\ absorbance} \times \frac{weight\ of\ standard}{100} \times \frac{5}{50} \times \frac{5}{50} \times \frac{200}{Sample\ weight} \times \frac{5}{50} \times \frac{5}{25} \times Average\ weight\ of\ tablet$$

$$\%Assay = \frac{drug\ content}{label\ claim} \times 100$$

4.5.9 STABILITY STUDIES [84, 85, 86]

Stability of a formulation can be defined as the time from the date of manufacture of the formulation until its chemical or biological activity is not less than a pre-determined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. Formulation and the development of pharmaceutical products are not complete without proper stability analysis. It is carried out to assess the physical and chemical stability and safety use of the product. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug products varies with the time under the influence of a variety of environmental factors such as temperature, humidity, and light enabling recommended for storage conditions and shelf life. The ICH guideline recommends the following storage conditions for stability studies:

Table No: 21: Stability conditions according to ICH guidelines

S. No.	Study	Storage Condition
1.	Long term	25°C±2°C / 60%RH±5%RH
2.	Intermediate	30°C±2°C / 65%RH±5%RH
3.	Accelerated	40°C±2°C / 75%RH±5%RH

4.5.10 Accelerated stability studies

Generally the observation of the rate at which the product degrades under normal room temperature requires a long time. The International Conference of Harmonization (ICH) Guidelines titled "Stability testing for new drug substances and product" (Q1A) describes the stability test requirements for drug registration application in the European Union, and United States of America. The accelerated stability was carry out by ICH guidelines.

The formulation F6 was packed in high density polyethylene container and kept at 40^0C ± 2^0C and 75% ± 5% RH. Samples were analyzed for drug content and *in-vitro* dissolution studies in the intervals of 1, 2, 3 months. The results of the stability studies are tabulated in ***Table No: 35, 36.***

CHAPTER 5

RESULTS AND DISCUSSION

5. RESULTS AND DISCUSSION

The present study was carried out to formulate colon targeted matrix tablet of Ibuprofen using direct compression method. In this method, the powder blend was subjected to various evaluation studies such as bulk density, tapped density, compressibility index and hausner's ratio and was compressed into tablets. The compressed tablets were evaluated such as thickness, hardness, friability, weight variation, assay, *in-vitro* dissolution studies, and accelerated stability studies. The tablets are coated using Enteric coating polymers (Eudragit FS 30 D) to target the release of pH 7.4. The uncoated and coated tablets are evaluated for *in-vitro* dissolution studies and the tablets are packed in bluster pack and were subjected to accelerated stability studies. The results are presented in appropriate tables and figures.

5.1 PREFORMULATION STUDIES:

The following preformulation studies were performed on Ibuprofen and excipients.

EVALUATION OF IBUPROFEN (API)

5.1.1 PHYSICAL CHARACTERISTICS OF API

Table No: 22

S. No	Tests	Specification	Results
1	Colour	White or off white powder	White or off white powder
2	Solubility	Practically insoluble in water, freely soluble in acetone, methanol and in methlyene chloride. It dissolves in dilute solution of alkali hydroxide and carbonates	Complies
3	Melting point	75.0° -78.0°C	76.4°C
4	Moisture content	NMT 0.5 w/w%	0.3% w/w

Discussion:

The colour, solubility, melting point and moisture content of the API were evaluated. It was found to be within the range of the monograph.

5.1.2 ANGLE OF REPOSE OF IBUPROFEN

Table No: 23

S. No	Raw material (API)	Angle of repose (Degree)	Average
1	Ibuprofen	38^0.14′	38^0.56′± 0.69
2	Ibuprofen	39^0.36′	
3	Ibuprofen	38^0.12′	

Discussion:

The angle of repose of API was found to be 38^0.56′± 0.69. Hence the drug belongs to fair flow and requires glidants to improve the flow property.

5.1.2.1 BULK DENSITY AND TAPPED DENSITY OF IBUPROFEN

Table No: 24

S. No	Raw material (API)	Bulk density (g/ml)	Average bulk density (g/ml)	Tapped density (g/ml)	Average tapped density (g/ml)
1	Ibuprofen	0.459	0.453 ± 0.01	0.612	0.614± 0.003
2	Ibuprofen	0.452		0.614	
3	Ibuprofen	0.448		0.618	

Discussion: The average bulk density and tapped density was found to be 0.453 ± 0.01 and 0.614± 0.003 g/ml respectively.

5.1.2.2 POWDER COMPRESSIBILITY AND HAUSNER'S RATIO

Compressibility Index and Hausner's Ratio

Table No: 25

Raw material (API)	Compressibility index (%)	Hausner's ratio
Ibuprofen	26.22	1.35

Discussion:

Based on Compressibility index and Hausner's ratio, it indicates the Ibuprofen (API) belongs to poor flow property.

5.1.2.3 PARTICLE SIZE DISTRIBUTION

PARTICLE SIZE DISTRIBUTION OF IBUPROFEN

Table No: 26

Sieve no	Empty weight of sieve	Quantity retained (gm)	Mass retained (gm)	Cumulative mass retained (gm)	Cumulative % retained	Percentage passing %
#20	367.8	368.55	0.75	0.75	4.34	95.66
#30	417.65	417.85	0.2	0.95	5.5	94.5
#40	358.05	365.65	7.6	8.55	49.56	50.44
#60	343.45	343.65	0.2	8.75	50.72	49.28
#80	340.75	340.9	0.15	8.9	51.59	48.41
#100	332.5	332.85	0.35	9.25	53.62	46.38
Base	540.45	548.45	8	17.25	100	0

Discussion:

From the particle size analysis it was concluded that the particles size of the API was found to be moderately coarse powder.

5.1.3 DRUG - EXCIPIENTS COMPATIBILITY STUDIES:

It was determined as per procedure given in material and method part. The following ***Table No: 27*** illustrates,

DRUG - EXCIPIENTS COMPATIBILITY

Table No: 27

S. No	Composition	Initial	After 15days	After 30days	Conclusion
1	Ibuprofen	White	NCC	NCC	Complies
2	Ibuprofen + Excipients	White	NCC	NCC	Complies

- **NCC-** No Characteristic Change.

Discussion:

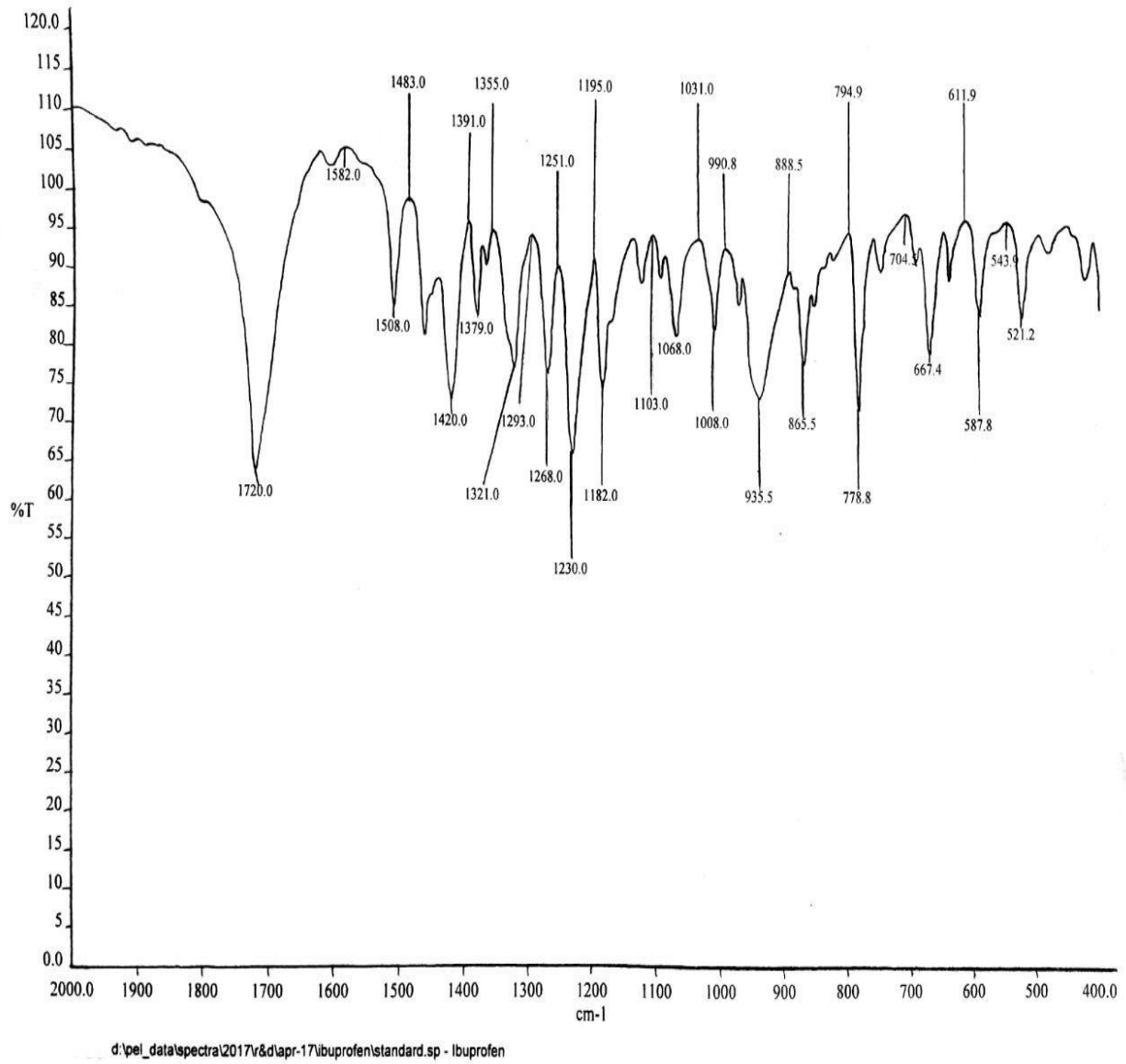
From the drug excipients compatibility study, it was observed that there was no characteristic change or interaction between drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Ibuprofen.

IR SPECTRAL ANALYSIS:

The FTIR studies of Ibuprofen and Ibuprofen with Excipients. The results are shown in Table No: 28, 29 Figure No: 9, 10.

FT-IR SPECTRA OF PURE IBUPROFEN

Figure No: 9



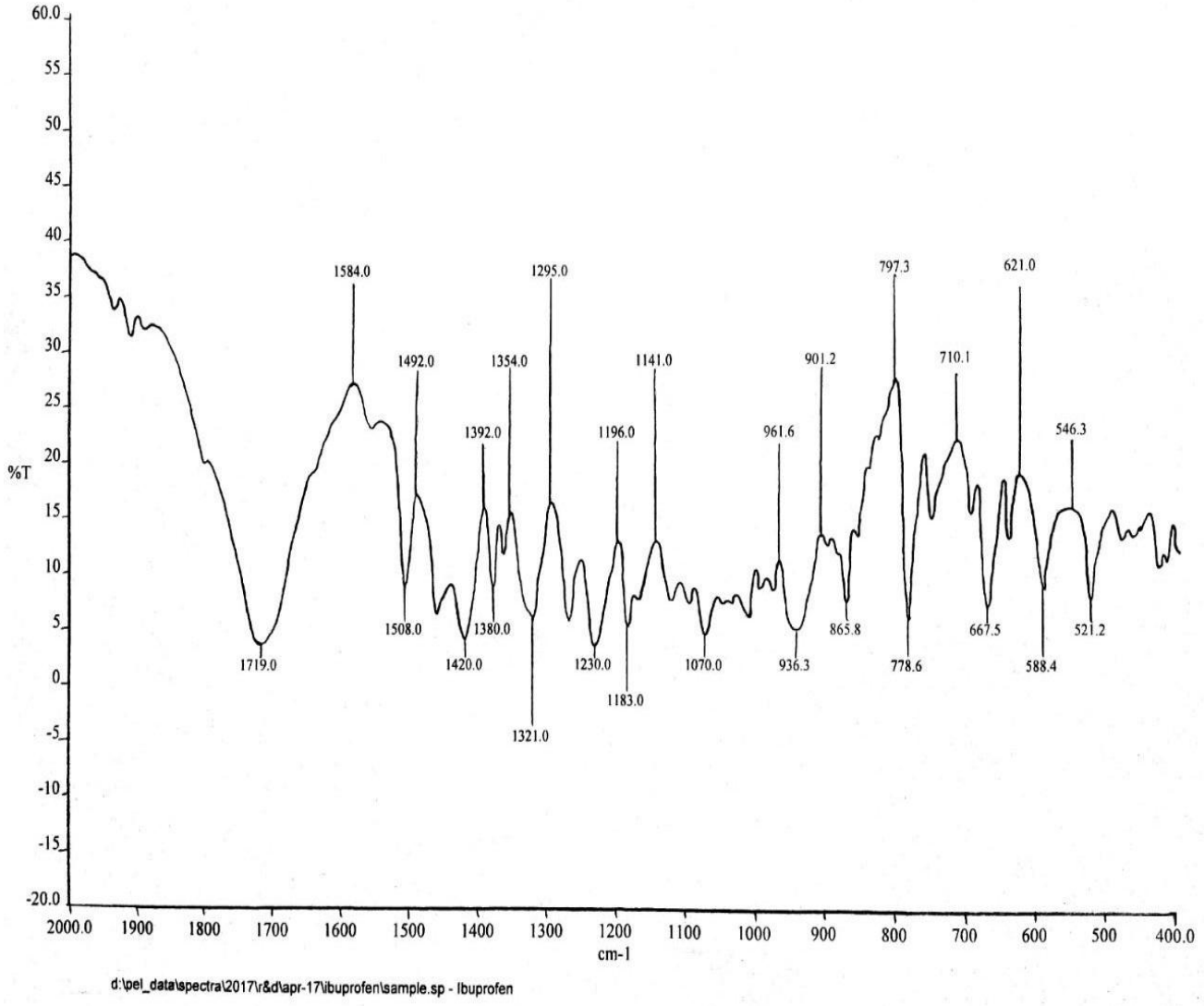
FT-IR SPECTRAL VALUES OF PURE IBUPROFEN

Table No: 28

S. No	Wave Number (cm^{-1})	Functional Group
1.	1720.0	C=O Stretching of carboxylic acid
2.	1420.0	C=C Stretching of Benzene
3.	1321.0	Methyl of alkane
4.	1230.0	Methylene of Benzene ring
5.	1068.0	C-O of carboxylic acid
6.	935.5	CH_2 bending vibration of alkane

FT-IR SPECTRA OF IBUPROFEN WITH EXCIPIENTS

Figure No: 10



FT-IR SPECTRAL VALUES OF IBUPROFEN WITH EXCIPIENTS

Table No: 29

S. No	Wave Number (cm^{-1})	Functional Group
1.	1719.0	C=O Stretching of carboxylic acid
2.	1420.0	C=C Stretching of Benzene
3.	1380.0	Methyl of alkane
4.	1230.0	Methylene of Benzene ring
5.	1070.0	C-O of carboxylic acid
6.	936.3	CH_2 bending vibration of alkane

Discussion:

Pure Ibuprofen spectra showed sharp characteristic peaks at 1720.0, 1420.0, 1321.0, 1230.0, 1068.0, 935.5 cm^{-1}. These peaks are also prominent in the FTIR spectra's of the physical mixtures containing Ibuprofen and other excipients in the final formula. This indicates that there is no interaction between the drug and excipients from both Physical observation and FT-IR studies.

5.2 EVALUATION OF LUBRICATED POWDER BLEND

Table No: 30

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio	Angle of repose (degree)	Moisture content (%)
F1	0.35±0.02	0.40 ± 0.01	11.73±0.79	1.12 ±0.15	$29^0$58'±0.53	1.15 ± 0.05
F2	0.31±0.03	0.35 ± 0.05	12.10±0.54	1.13 ±0.28	$33^0$23'±0.35	1.28 ± 0.02
F3	0.37 ± 0.01	0.42 ± 0.06	13.63±0.38	1.13 ±0.12	$30^0$96'±0.19	1.42 ± 0.02
F4	0.38 ± 0.07	0.40 ± 0.08	11.57±1.05	1.14± 0.85	$31^0$26'±0.60	1.21 ± 0.06
F5	0.35 ± 0.10	0.44 ± 0.06	12.60±0.86	1.12 ±0.74	$29^0$35'±0.48	1.33 ± 0.03
F6	0.41± 0.06	0.46± 0.01	12.98±0.65	1.13 ±0.24	31^0.05'±0.25	1.15 ± 0.02

All values are expressed as mean ± standard deviation, n=3

Discussion:

The lubricated powder blends was evaluated for different parameters and the results are given in ***Table no: 30.***

- The bulk density and tapped density of all formulations were measured by using graduated measuring cylinder. The bulk density was found in the range of 0.31-0.41gm/cm^3. The tapped density was between 0.35-0.46 gm/cm^3. Both are within the acceptable limits.
- If the compressibility index of the powder is between 11 and 15, it shows good flow character, here all the formulations exist in the range between 11.73-13.63. It indicates that the granules showed good flow character.
- The result showed that the Hausner ratio of all the formulations was between 1.12-1.14, if the Hausner ratio lies between 1.12-1.18, it shows good flow behavior of the granules or powder. The result indicates good flow property of the granules.

- If the angle of repose is within 35^0, it indicates good flow property of the granules. The result showed that the angle of repose of all the formulations was between 29^0-33^0.It proved that the flow properties of all formulations are good.

5.3 EVALUATION OF FINISHED PRODUCT (UNCOATED)

Table No: 31

Parameters	F1	F2	F3	F4	F5	F6
Average weight (mg)	450±1.18	450±0.89	450±2.00	450±0.61	450±2.68	450±0.21
Thickness (mm)	3.4± 0.16	4.2±0.09	4.7± 0.14	5.9± 0.12	5.7±0.01	5.9 ± 0.16
Hardness (kg/cm^2)	12.6 (± 0.15)	9.4 (± 0.22)	6.2 (± 0.30)	5.2 (± 0.32)	6.0 (± 0.30)	5.8 (± 0.11)
Friability (%)	0.36	0.41	0.39	0.31	0.35	0.33
Disintegration time (min)	-	24’46’’	17’42’’	14’45’’	8’42’’	7’18’’
Assay (%)	99.34	99.2	98.51	99.85	99.53	100.21

All values are expressed as mean ± standard deviation, n=3

Discussion:

The tablets are evaluated for different parameters are given in ***Table no: 31.***

- The thickness of the tablets was in the range of 3.4 to 5.9 mm. This is due to the upper and lower punch adjustments during compression process.
- The prepared tablets in all the trials possessed good mechanical strength with sufficient hardness in the range of 12.6 to 5.2 kg/cm^2.

- The friability of the tablets was found to be within 1%. All the above trail formulations have passed the friability test.
- The average weight of all the formulations was found to be 450mg. It is within the permissible range.
- The percentage of drug content was found among different batches of the tablets and ranged from 98.5 to 100.21 which were within the acceptable limits.

5.4 EVALUATION PARAMETERS OF IBUPROFEN ENTERIC COATED TABLETS

Table No: 32

Trial	Thickness (mm)	Weight variation (mg)	Disintegration time(min)	Assay (%)	Drug release (%)
F6	6.0 ± 0.02	477±0.21	218'63'' ±1.98	99.92 ± 0.08	98.51

All values are expressed as mean ± standard deviation, n=3

Discussion:

Ibuprofen tablet of the above trial (F6) was satisfied of all the parameters. It was coated by using enteric coating method. The coated tablets were evaluated for the following parameters including thickness, disintegration test, weight variation, assay and *in-vitro* studies.

5.5 COMPARATIVE DATAS OF UNCOATED AND ENTERIC COATED IBUPROFEN TABLETS

Table No: 33

Trial	Thickness (mm)	Weight variation (mg)	Assay (%)	Drug release (%)
F6 Un coated	5.9 ± 0.16	451±5	100.21±0.12	99.69 at 12 hrs
F6 Enteric coated	6.0±0.02	477±5	99.92 ± 0.08	98.51 at 24 hrs

All values are expressed as mean ± standard deviation, n=3

Discussion:

Ibuprofen Enteric coated tablets were compared with the same trial of uncoated Ibuprofen tablets. The thickness of Enteric coated tablets was found to be more than uncoated tablets. Weight variation was increased in Enteric coated tablets than the uncoated tablets. This is due to the coating of core tablet.

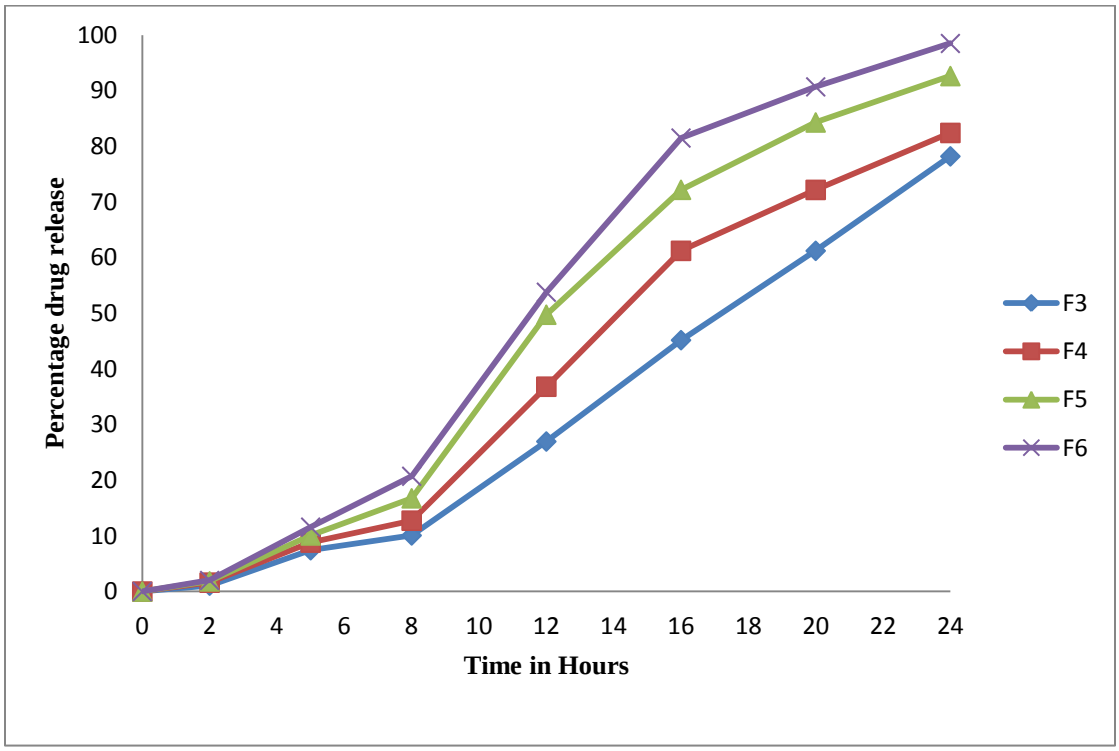
5.6 *IN-VITRO* DISSOLUTION PROFILE OF ENTERIC COATED TABLETS

Table No: 34

Dissolution Media	Sampling time	Cumulative% drug release in different trials			
		F3	F4	F5	F6
Simulated gastric fluid (0.1 HCL)	2 Hrs	1.07	1.60	1.83	2.00
Simulated Intestinal Fluid (7.4pH Phosphate buffer)	5 Hrs	7.43±0.32	8.804±0.13	10.09±0.78	11.58±0.13
	8 Hrs	10.09±0.78	12.74±0.43	16.76±0.13	20.72±0.43
	12 Hrs	26.97±0.52	36.82±1.35	49.76±0.57	53.80±0.78
	16 Hrs	45.18±0.95	61.24±0.52	72.21±0.95	81.51±0.57
	20 Hrs	61.24±0.57	72.19±0.43	84.31±0.57	90.71±0.95
	24 Hrs	78.22±0.78	82.43±0.57	92.65±0.95	98.51±0.78

Figure No: 11

Graphical representation of *in-vitro* drug release



Discussion:

F1: The method used in this trial is direct compression. The concentration of Eudragit S 100 used was 80 mg/unit, Ethyl cellulose concentration was 60mg/unit. Lactose DCL 21 was 50mg/unit. And the concentration of Talc and magnesium stearate used was 5mg/unit. The hardness of the tablet were crossed the specification limit.

F2: Same as procedure of F1. But in this formulation the concentration of Eudragit S100 and Ethyl cellulose was decreased to 60 mg/unit and 55mg/unit. And diluent concentration increased to 75mg/unit. The hardness of this formulation were better than the above formulation but the time required to disintegrate tablets were crossed the specification limit.

F3: The hardness were achieved. But the time required to disintegrate tablets were crossed the specification limit. In this formulation the concentration of Eudragit S100 and Ethyl cellulose was decreased to 50 mg/unit and 40 mg/unit to reduce the hardness of the tablets. And the diluent concentration increased to 100mg/unit. This formulation was selected for coating. And the

tablets were subjected to *in-vitro* dissolution study. The release was found to be 78.22±0.78 at 24 hrs.

F4: In trial 4 the concentration of Eudragit S100 and Ethyl cellulose was further decreased to 35mg/unit and 25mg/unit and increased the Lactose DCL21 concentration to 130mg/unit. The disintegration time of tablet was better than the above formulations but crossed the limits. The tablets were subjected to *in-vitro* dissolution study.

F5: The concentration of Eudragit S100 and Ethyl cellulose was further decreased to 20mg/unit and 15mg/unit and increased the Lactose DCL21 concentration to 154mg/unit. The concentration of Magnesium stearate was increased to 6mg/unit to improve the lubrication of granules. The disintegration time of tablet was found to be within the limit. The triethyl citrate was used in the enteric coating part, to give better flexibility to the polymer. The tablets are subjected to *in-vitro* dissolution study. The percentages of drug release were found to be 92.65±0.95 at 24 hrs. It was better than the earlier trials.

F6: The concentration of Eudragit S 100 and Ethyl cellulose was further decreased to 14mg/unit and 10mg/unit and increased the Lactose DCL21 concentration to 165mg/unit. The tablets of this trial are subjected to *in-vitro* dissolution study. The percentage of drug release showed 98.51±0.78 at 24 hrs. This trial was taken as confirmatory trial and subjected as stability studies.

5.7 STABILITY STUDIES

5.7.1 PHYSICAL PARAMETERS

Stability studies for post compression parameters of (F-6) enteric coated tablets

Table No: 35

Post compression Parameters	Storage condition: 40^0C± 2^0C /75±5%RH			
	Initial	1st month	2nd month	3rd month
Description	White coloured Enteric coated tablet	White coloured Enteric coated tablet	White coloured Enteric coated tablet	White coloured Enteric coated tablet
Average weight (mg)	477±0.21	477.38 ± 0.003	477.52 ± 0.006	477.67 ± 0.04
Disintegration time (minutes)	219’63’’±0.03	219’13’’±0.08	220’ 38’’±0.08	221’ 7’’ ±0.05

*All the values are expressed as mean’s, n=3.

Discussion:

The F-6 formulation of enteric coated tablets was carried out for the stability study. It was kept at 40^0C± 2^0C /75±5%RH. It revealed that there were no significant changes in color but slight increase in average weight and disintegration time. The sample was tested at one month interval.

5.7.2 *IN-VITRO* DRUG RELEASE AND ASSAY

Table No: 36

Formulation	Time in hrs	Storage condition $40^0C \pm 2^0C$ /75±5%RH					
		In-vitro drug release (%)				Assay (%)	
		Initial	1 month	2 month	3 month	Initial	After Stability
F6	24	98.51	98.31	97.42	97.28	100.21	100.1

Discussion:

The F6 formulation of enteric coated tablets was carried out for the stability study, it was kept in $40^0C \pm 2^0C$ /75±5% RH for the period of three months. Percentage of drug release and assay was determined. The data's does not showed much variation during stability studies. The results revealed that the product was stable.

CHAPTER 6

SUMMARY AND CONCLUSION

6. SUMMARY AND CONCLUSION

The present work involves the formulation of colon targeted matrix tablet of Ibuprofen by using direct compression method. Literatures regarding, Ibuprofen tablet dosage form preparation, excipients selection, manufacturing method, etc., has been collected and reviewed.

In this work, selection of excipients was done based on a literature review. Excipients include Eudragit S100, Ethyl cellulose, Lactose, Talc, Magnesium stearate. Quantities of the excipients were selected by performing FT-IR method which is an IHS of Fourrts India Laboratory.

Preformulation studies have also been performed to study the nature of API and compatibility of API with excipients by physical observation and FT-IR studies. The result showed that API was compatible with all the excipients selected.

The tablets were formulated by direct compression method using the selected excipient quantities. The formulated tablets were tested for both pre-compression parameters and post compression parameters as per requirements of standards. Pre-compression parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and compressibility index. The results obtained indicate that it has good flow property for direct compression.

The formulated Ibuprofen matrix tablets were coated with enteric polymer Eudragit FS 30D by pan coating method. The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, disintegration time and *in-vitro* dissolution studies. All these parameters were found to be within the standard limits.

Comparative studies of coated Ibuprofen tablets and uncoated Ibuprofen tablets are evaluated for the hardness, thickness, *in-vitro* dissolution studies and disintegration time.

Out of six formulations, the formulation F6 showed 98.51% drug release at 24 hrs. Since it provide greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. So the formulation F6 was considered as the confirmatory trial and it was subjected for stability studies up to three months of accelerated stability $40^0C \pm 2C^0$, 75 % ± 5 % RH and found to be within limits.

CONCLUSION

Preformulation studies were performed to study the nature of API and compatibility of API with excipients by physical observation and FT-IR studies. The results showed that there was no interaction between API and all the excipients selected.

The Ibuprofen matrix tablets were successfully formulated by direct compression method using the selected excipient quantities. The formulated tablets were evaluated for both pre-compression and post-compression parameters as per requirements of standards. And the results were complied with the pharmacopoeia specification. The formulated Ibuprofen matrix tablets were coated with enteric polymer Eudragit FS 30D by pan coating method.

From among the entire batches, formulation F6 showed 98.51% drug release at 24 hrs. Since it provide greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. So the trial F6 was considered as best formulation. From the results obtained, it can be concluded that formulation F6 containing enteric coated matrix tablet of Ibuprofen would be a promising formulation to achieve the purpose which treat inflammatory bowel diseases (ulcerative colitis) without any gastric irritation or ulcers, which is useful for patients having pre history of ulcerative colitis.

CHAPTER 7

FUTURE STUDY

7. FUTURE STUDY

The finding of the present study has initiated the company to go in for scale up trial. Based on the reproducible results produced from batch to batch the company will decide to launch the product in the future.

CHAPTER 8

BIBLIOGRAPHY

8. BIBLIOGRAPHY

1. Ansel H, Allen L and Jr. Popovich N. Ansel's Pharmaceutical Dosage Forms and Drug delivery systems, Baltimore, Md: Lippincott Williams & Wilkins. 8th edition, 2004; p.g 260-268.
2. Leon Lachmann, Herbert A. Liberman, Joseph L Kanig. The Theory and Practice of Industrial Pharmacy.Varghese publishing House,Bombay, 3rd edition, 1998: p.g. 171, 201-213, 285-286, 293, 313-314, 400-456.
3. Chien Y.W. Novel Drug Delivery Systems. Revised and expanded, 2nd edition: 1992: p.g 1-2, 139-140.
4. Mehta R.M. Pharmaceutics-1.Vallabh Prakashan, 3rd Edition New Delhi: 2002: p.g. 238-239.
5. Indian pharmacopoeia. The Indian Pharmacopoeia Commission.Ghaziabad: 2007 Vol.2 p.g 662.
6. Debjit Bhowmik. Tablet manufacturing processs and defects of tablets, Elixir Pharmacy 70 (2014) p.g. 24368-24374.
7. Leon Lachmann, Herbert A. Lieberman, Joseph L. Kanig, The Theory and Practice of Industrial Pharmacy, New Delhi,CBS publishers, 4th edition,2006: p.g. 293-303.
8. David Jones, Pharmaceutics Dosage form and Design,. Pharmaceutical Press London, Chicago, 2008, 1st edition p.g: 227.
9. Gilbert.S.Banker, Christopher. T.Rhodes, Modern Pharmaceutics, 4th edition, NewYork. Basel, 1980, p.g:17.
10. Lachman.L, Liberman H.A, Joseph L Kanig. The Theory and Practice of Industrial pharmacy. Varghese publishing house, New Delhi, 3rdedition, 1989; p.g. 331-332.
11. James.W, Linda A.F. Aqueous Polymeric Coating for Pharmaceutical Dosage forms. Taylor and Francis, p.g.327.
12. Alford N Martin, Patrick J. Sinko. Martin's Physical pharmacy and pharmaceutical sciences, Lippincott Williams & Wilkins. 6th edition 2006.p.g 302
13. Lachman.L, Lieberman H.A, Joseph L Kanig. The Theory and Practice of Industrial Pharmacy, Varghese publishing house, 3rd edition, 1990; p.g 346.

14. Sayed I. Abdel-Rahman, Gamal M.M, El-Badry M, Preparation and Comparative Evaluation of Sustained Release Metoclopramide Hydrochloride Matrix Tablets, Saudi Pharmaceutical Journal ,2009 ; 17: p.g 283-288.
15. Chandran S, Laila F.A and Mantha N, Design and Evaluation of Ethyl Cellulose Based Matrix Tablets of Ibuprofen with pH Modulated Release Kinetics, Indian Journal of Pharmaceutical Sciences, September-October 2008.
16. Gothi G.D, Parinh B.N, Patel T.D, Prajapati S.T, Patel D.M, Patel C.N, Journal of Global Pharma Technology, 2010; 2(2):p.g 69-74.
17. Basak S.C, Reddy J.B.M, and Lucas Mani K.P. Indian Journal of Pharmaceutical Sciences, September-October 2006.
18. Varshosaz J, Tavakoli .N and Kheirolahi. A.A.P.S PharmSciTech, 2006; 7(1).
19. Raghvengra Rao N.G, Gandhi S, and Patel T. International Journal of Pharmacy and Pharmaceutical Sciences, 2009; 1(1).
20. Shivhare U.D, Adhao N.D, Dr. Bhusari K.P, Dr. Mathur V.B and Ambulkar U.D. International Journal of Pharmacy and Pharmaceutical Sciences, 2009; 1(2).
21. Vyas S.P, Khar R.K. Controlled Drug Delivery: Concepts and Advances. 1st edition. Vallabh Prakashan, 2002:p.g.156-189.
22. Brahmankar H.A, Jaiswal S.B, Biopharmaceutics and Pharmacokinetics a Treatise, Vallabh Prakashan, 2000, p.g 348-357 and 337.
23. Wani M.S, Controlled Release System- A Review, 2008, 6 (1), www.pharmainfo.net/review
24. Philip A.K, Dabas S, Pathak K. Optimized Prodrug Approach: A means for achieving enhanced Anti-inflammatory Potential in Experimentally Induced Colitis. Journal of Drug Target 2009; p.g 17:235-241.
25. Oluwatoyin A.O, John T.F. *In vitro* evaluation of Khaya and Albizia gums as Compression Coating for Drug Targeting to the Colon. Journal of Pharm Pharmacol 2005; 57:p.g. 63-168.
26. Akala E.O, Elekwachi O, Chase V, Johnson H, Lazarre M, Scott K. Organic Redox-initiate, Polymerization Process for the Fabrication of Hydrogels for Colon-specific Drug Delivery. Ind Pharm. 2003; 29(4): p.g 375-386.
27. Chourasia M.K, Jain S.K. Pharmaceutical Approaches to Colon Targeted Drug Delivery Systems. Journal of Pharmaceutical Science 2003; 6: p.g 33-66.

28. Wood E, Wilson C.G, Hardy J.G. The spreading of foam and solution enemas. International Journal of Pharmacy 1985; 25:p.g 191-197.
29. Singh N, Khanna R.C. Colon targeted drug delivery systems – A Potential Approach. The Pharma journal. Vol. 1 No. 1 2012.
30. Quresh Altamash M, Momin Munira, Rathod Sudha, Dev Asish, Kute Chaitrali. Colon targeted drug delivery system: A review on current approaches. Indian Journal of Pharmaceutical and Biological Research. 2013; 1(4):p.g 130-147.
31. Biswal P.K, Kumar A , Bhadouriya AS. Design and evolution of colon specific drug delivery system. . 2013; 3:1:p.g 150-167.
32. Sonasaniya Balvir, Dr. M.R. Patel, Dr. K.R.Patel, Dr. N.M. Patel. A Review on colon targeted drug delivery system. International Journal of Universal Pharmacy and Bio Sciences. 2013; 2(1):p.g 20-34.
33. Pramod Kumar Biswal, Anant Kumar and Anupam Singh Bhadouriya. Design and evolution of colon specific drug delivery system. IJPCBS. 2013; 3:1. p.g 150-167
34. Malik K, Goswami L, Kothiyal P, Mukhopadhyay S.A Review on Colon targeting Drug Delivery System: Novel Approaches, Anatomy and Evaluation. The Pharma Innovation. 2012; 1(9): p.g 1-12.
35. John wiley and sons, Inc. Encyclopedia of controlled drug delivery, Newyork, 2003, p.g 698-726
36. Sarasija S, Hota A. Indian J Pharmaceutical Sci. 2000; 62:p.g 1-8.
37. Reena Sharma, Nimrata Seth. Colon Targeted Drug Delivery System: A review.2013: 4:4: p.g 66-77.
38. Vyas S.P, Khar R.K. Controlled Drug Delivery Concepts and Advances. New Delhi; Vallabh Prakashan: 2nd edition, 2012, p.g. 218-227.
39. Prasad K, Badarinath A.V, Anilkumar P, Reddy B.R, Naveen N, Nirosha M, Hyndavi M. Colon Targeted Drug Delivery Systems: A Review. Journal of Global Trends in Pharmaceutical Sciences, 2011; 2(4):p.g 460 and 461.
40. Baumgart DC, Carding SR (2007). "Inflammatory bowel disease: cause and immunobiology." The Lancet. 369 (9573):p.g 1627–40.

41. Shanahan F. Ulcerative colitis. In: Hawkey C.J, Bosch J, Richter J.E, Garcia- Tsao G, Chan F.K.L,Textbook of Clinical Gastroenterology and Hepatology. 2nd edition. Oxford: Wiley-Blackwell; 2012:p.g 355–371.
42. KoY, Butcher R, Leong RW. Epidemiological studies of migration and environmental risk factors in the inflammatory bowel diseases. World Journal of Gastroenterology. 2014; 20(5): p.g. 1238–1247.
43. Pathogenesis and Treatment of Ulcerative Colitis JMAJ 46(6): 2003 p.g. 257–262,
44. NehaSingh, Raghuvanshi, Laxmi Goswami, Preeti Kothiyal. Formulation and evaluation of colon targeted dosage form of prednisolone tablet using sterculia gum. Journal of applied pharmaceutical research sep-2014, ISSN No. 2348 – 0335.
45. Sumit Kumar, Anurag Bhargava Formulation and Evaluation of Matrix Tablets of Naproxen for Colon Targeting Asian Journal of Biomedical and Pharmaceutical Sciences 2(11) 2012, 28-31.
46. Biresh Kumar Sarkar, Jain DA1 and Vikram Sharma Formulation and Evaluation of Flurbiprofen Matrix Tablets for Colon Targeting, International journal of pharmaceutical and chemical sciences Vol. 1 (2) Apr – Jun 2012.
47. Sharma Madhu, Joshi Baibhav, Bansal Monika, Goswami Manish, formulation and evaluation of colon targeted tablets of mesalazine, Journal of Drug Delivery & Therapeutics; 2012, 2(5), 24-36.
48. R.Prashanthi, P.Naga Haritha, E.Hima Bindu, P.Sunil Kumar Chaitanya, Akram Khan, formulation and in – vitro evaluation of controlled release matrix tablets of flurbiprofen, Indo American Journal of Pharmaceutical Research, 2014, Vol 4, Issue 12, 2014.
49. Lone Krishnakumar Devrao, Dhole Jyoti Arjunrao and Dhole Nagesh Arjunrao. Formulation and Evaluation of Matrix Tablet of Mesalazine with Hydroxypropylmethylcellulose Phthalate, International journal of pharmaceutical and chemical sciences, Vol. 1 (4) Oct-Dec 2012.
50. Rajeswari P, Kiranmai T., Manthrunaik D., A. V. Suresh Babu, Sunil Kumar M,. Subbarao G., Gopaiah K., Dr. Sudhakara Rao G. Formulation and characterization of colon specific drug delivery system of a matrix tablet. wjpls, 2016, Vol. 2, Issue 2, 330-348.

51. Prasanta kumar choudhury, padala narasimha murthy, niraj kanti tripathy, b. sanuja patra, formulation design and development of enteric coated matrix tablets of ornidazole for colonic delivery Asian Journal of Pharmaceutical and Clinical Research Vol 5, Suppl 3, 2012.
52. Basavaraja, Kirankumar Navade, B.Someswara Rao, Suresh V. Kulkarni, Formulation and Evaluation of Sustained Release Matrix Tablets of Flurbiprofen by Using Naturaland Synthetic Polymers. J. Pharm. Sci. & Res. Vol. 7(6), 2015, 274-281.
53. B.manjula, V.aishwarya, Vinod beulah, Y. Sudheer kumar, A. Bharathi and Ashok, formulation and evaluation of ornidazole matrix tablets for colon specific drug delivery, world journal of pharmacy and pharmaceutical sciences, Volume 5, Issue 4,p.g. 2440-2449.
54. L.matsyagiri, B.Premkumar, D.Pranitha, P.Venukumar, Design and Evaluation of Albendazole matrix tablets for colon specific drug release.adv pharm life sci Res, 2014 2;4: p.g.17-28.
55. Patel Jayvadan K., Patel Nirav V, Shah Shreeraj Formulation and *in-Vitro* evaluation of mesalamine matrix tablets using chitosan for colonic drug delivery, Journal of Pharmacy Research 2009, 2(8), p.g 1319-1323.
56. PrasanthV.V , Jayaprakash R, Sam T Mathew, Rinku Mathappan, and Sourav Tribedi, Formulation and Evaluation of Matrix Tablets of Albendazole for Colon Site Specific Drug Delivery, Research and Reviews in Pharmacy and Pharmaceutical Sciences, e-ISSN:2320-1215 p-ISSN: 2322-0112.
57. Shakhar singh,Sandeep singh,Dheeraj sood,Jasveer singh, Formulation and optimization of flurbiprofen matrix tablets for colonic drug delivery, International journal of pharma professional's Research.October 2013, Volume-4,Issue-4.
58. K.Ramesh Reddy, C.P. Sreekanth Reddy, G.Saisri Harsha, V.Jayasankar Reddy P. Jayachandra Reddy, K. Anil. Formulation and Evaluation of Prednisolone Matrix Tablets for Colon Targeted Drug Delivery System, Indo american journal of pharmaceutical sciences, 2015, Vol 2 (4), p.g. 863-869.
59. G. Subba rao and Tegk murthy, Formulation and Evaluation of Diltiazem Hydrochloride Colon Targeted Tablets, International journal of research in pharmacy and chemistry, IJRPC 2013, 3(4), ISSN:p.g. 2231-2781.

60. Satinder Kakar, Ramandeep Singh, Ramandeep Kaur, Alok Semwal, Preparation and drug release assessment of mesalazine matrix tablets, International Journal of Pharmaceutical and Medicinal Research, Res. 2014; 2(1):p.g.28-32.
61. Prasanta Kumar Choudhury, Padala Narasimha Murthy, Niraj Kanti Tripathy, B. Sanuja Patra, Design and development of colon-specific drug delivery system for orally administered ornidazole, International Journal of Universal Pharmacy and Life Sciences 2(1): January-February 2012.
62. Magdum Sonali Vijaykumar, Nitave Sachin A, Choundikar Mayuri Y, Mujawar Nigar K, formulation and evaluation of colon targeted tablet of budesonide, Journal of drug delivery research, Volume 5 Issue 2 2016.
63. Dr. T. Satyanarayana, Jogu Jameema, Kumarraja Jayavarapu, B. Saraswathi and K. Lalitha, Formulation and Evaluation of Mesalazine Colon Targeted MatrixTablets, Pharma Research Library Friday , 24 February 2017.
64. Srilakshmi.N, P.Sobhita Rani, Monica Revival,Arun Kumar Das, Formulation and Evaluation of Metronidazole Enteric Coated Tablets for Colon Targeting, Ijppr. Human, 2015; Vol. 3 (2): p.g.78-92.
65. J. R. Jadhav, K. S. Salunkhe, G. D. Burute, S. R. Chaudhari**,** Formulation and evaluation of colonic compression coated tablet of budesonide, Journal of Pharmacy Research 2012, 5(5), p.g.2783-2788.
66. Indian Pharmacopoeia, vol-1.Govt of India, Ministry of Health and Family Welfare, New Delhi: 1996; p.g. 387-388.
67. Indian Pharmacopoeia, vol-11.Govt of India, Ministry of Health and Family Welfare, New Delhi: 2007; p.g. 1217.
68. British Pharmacopoeia, vol-1. Department of Health and Social Security, Ministry of Health and Social Services for Northern Ireland: 1988; p.g.307.
69. Sengupta.P.R "Medical Pharmacology" 2nd Edition; CBS Publishers, New Delhi: 2010; 324.
70. Goodman and Gilman's,"The Pharmacological Basis of Therapeutics", 9th edition; McGraw-Hill Companies,New Delhi : 1996 p.g.;639.
71. Peter. H. Johnson and Patricia Nale, Pharmacist's Drug Hand Book, American Society of Health System, Maryland: 2001; p.g. 589-590.

72. "CIMS",Updated Prescribers Hand Book.CMP Medica India (P) Ltd,Bangalore; 2008;Apr-July,p.g. 222-223.
73. Rang H.P and Dale M.M, "Pharmacology", 2nd edition; ELBS Publishers, London: 1988; p.g. 207.
74. PadmajaUdaykumar,"Text book of Medical Pharmacology",2nd edition; CBS Publishers,New Delhi:2006;p.g 234.
75. Arthur H. Kibbe, Hand book of pharmaceutical excipients 3rd edition Pharmaceutical press.
76. Steele G. Preformulation as an aid to product design in early drug development. In Gibson M, editor. Pharmaceutical Preformulation and Formulation: A Practical guide from Candidate Drug Selection to Commercial Dosage Form.: p.g. 175.
77. Carr.R.L, Evaluation of flow properties of granules, Chem.Eng. 1965, p.g: 72,163- 168.
78. Bulk Density and Tapped Density. In USP 30 NF 25.; 2007. p.g. 643.
79. Powder Flow. In USP 30 NF 25.; 2007. p.g. 688-690.
80. Staniforth J. Powder Flow. In Aulton ME, editor. Pharmaceutics: The Science of Dosage Form Design. 2nd ed.: Churchill Livingstone. p.g. 207
81. Powder Flow. In USP 30 NF 25.; 2007. p. 688-690. Banker GS, Anderson NR. Tablets. In Lachman L, Lieberman HS, Kanig JL, editors. The Theory and Practice of Industrial Pharmacy. Varghese Publishing House. p.g. 296-301.
82. Friability Test. In Indian Pharmacopoeia.: Government of India; 2010.
83. Weight Variation Test. In USP 30 NF 25; 2007.p.g.731.
84. Stability testing of active substance and pharmaceutical products. WHO Organization, 2006; p.g: 1211, 27:12-30.
85. Hadkar, U.B. Physical Pharmacy. Nirali Prakashan. Pune, 8th edition, 2008, p.g: 20.
86. ICH guideline, European Medicines Agency, 2003: CPMP/ICH/2736/99.